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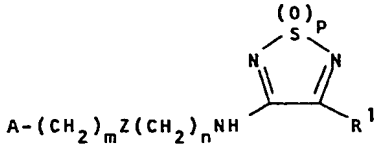
(54) **Pharmaceutical compositions.**

(57) Enhanced antiulcer activity is obtained in warm-blooded animals by the concomitant administration of the pepsin complexing agent, pepstatin, and an histamine $H_2$-receptor antagonist of the formula



wherein A, m, Z, n, p and $R^1$ are as defined herein. Concomitant administration of the two entities reduces the amount of histamine $H_2$-receptor antagonist necessary for treatment, thereby decreasing its side-effect liability.

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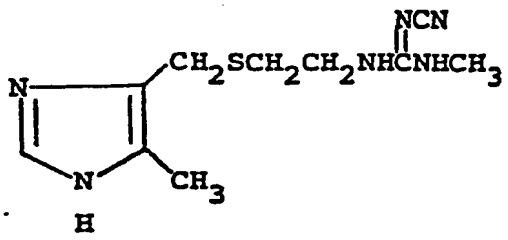
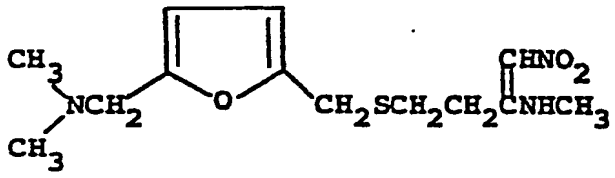
all secretagogues could be antagonized by specific antagonists of these receptors [Black, J. W. et al., Nature, 236, 385-390 (1972); Brimblecombe, R. W. et al., J. Int. Med. Res., 3, 86-92 (1975)]. The first successful commercial histamine $H_2$-receptor antagonist, cimetidine (II),



II

is now in widespread use as an antiulcer agent. A more recently introduced histamine $H_2$-receptor antagonist, ranitidine (III),



III

is now being sold and used in several countries of the world.

The role of the proteolytic enzyme, pepsin, in the etiology of ulceration is not completely understood. Pepsin has been shown to play a major role in the development of experimentally induced ulcers in animals, but this may be due to lesion enlargement by means of pepsin digestion of necrotic tissue rather than by causing the initial damage. It is also possible that pepsin is entirely responsible for the erosions and that the acid produces pain and retards healing.

1) Umēzawa, H. et al., in J. Antibiotics, 23, 259-262 (1970), disclose the pentapeptide, pepstatin, which has the structure

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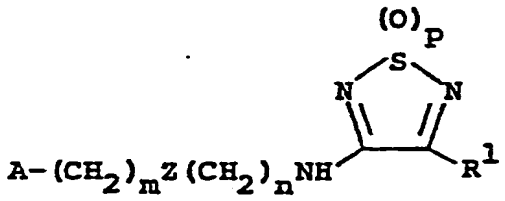
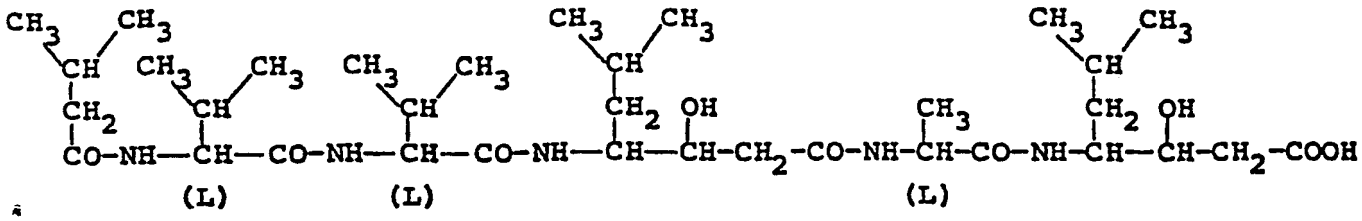
In the treatment of peptic ulcers in warm-blooded animals, the concomitant administration of the pepsin-complexing agent, pepstatin, and an histamine $H_2$-receptor antagonist of the formula I:



I

wherein A, m, Z, n, p and $R^1$ are as defined below, provides enhanced antiulcer activity, reduces the amount of the compound of Formula I necessary for effective treatment and thereby reduces the side effect liability of the compound of formula I. This invention relates to pharmaceutical compositions containing pepstatin and at least one compound of Formula I for treating peptic ulcers in warm-blooded animals.

The precise cause of peptic ulceration in man is unknown although gastric acid is considered to be one of the essential factors in the etiology of this disease. It recently was discovered that gastric acid secretion is mediated, at least in part, by histamine $H_2$-receptors located on parietal cells in the gastric mucosa and that gastric acid output induced by



and which is a specific complexing agent for the enzyme pepsin. Pepstatin was found to prevent the formation of stomach ulcers in the pylorus ligated (Shay) rat.

2) Miyawaki, et al., in Nagano-ken Noygo Sogo Shikenjo Chikusan Shikenjo Kenkyu Hokoku, 14, 14-25 (1977) [as reported in Chemical Abstracts, 90, 34373X (1979)] report that the addition of pepstatin to the feed at >50 ppm inhibited pepsin activity in the gastric juice of swine and prevented the occurrence of ulcers.

3) Bonnevie, O. et al., in Gut, 20, 624-628 (1979), report the results of a double-blind randomized clinical trial of pepstatin versus placebo in patients having duodenal ulcers. Pepstatin was administered in 100 mg doses, given seven times a day, this dosage being sufficient to inhibit the peptic activity of gastric juice for 18 hours a day. They found no significant difference between pepstatin and placebo in the healing or symptomatology of duodenal ulcer.

4) Svendsen, L. B. et al., in Scand. J. Gastroent., 14, 929-932 (1979), report the results of a double-blind randomized clinical trial of pepstatin versus placebo in patients having gastric ulcer. Pepstatin was administered in 100 mg doses seven times a day. They were not able to detect any influence of pepstatin either on the healing or on the symptomatology of gastric ulcer.

5) Strauss, R. J. et al., in Surg. Forum, 28, 361-363 (1977), disclose that, in stress ulceration tests in rats, two or more days of pretreatment with either cimetidine or carbenoxolone significantly decreased ulcer formation. When the two agents were given together, significant ulcer reduction

was found after only one-half day of predosing. Carbenoxolone is not an antisecretory or anti-pepsin agent, but acts by stimulating gastric mucus synthesis.

6) Dajani, E. Z. et al., in J. Pharmacol. Exp. Ther., 210, 373-377 (1979), disclose that, in stress ulceration tests in rats, a combination of cimetidine and propantheline bromide produced synergistic antiulcer activity and that a combination of cimetidine and thiopropazate hydrochloride produced additive antiulcer activity. Propantheline bromide (an anticholinergic agent) and thiopropazate hydrochloride (a tranquilizer) each act by inhibiting gastric secretion.

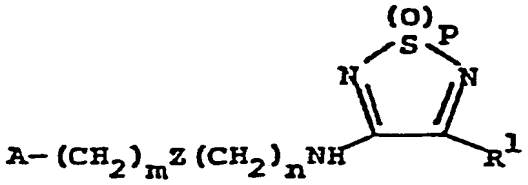
7) British Medical Journal, 95-96 (1980) reviews the results obtained in a large number of studies with various new antiulcer agents. With regard to pepsin antagonists, it states:

> "The results of using pepsin antagonists have been uniformly disappointing. Amylopectin showed no significant benefit in patients with duodenal ulcer, and sucralfate showed none in those with gastric ulcer. Even pepstatin, the most potent in-vitro and in-vivo pepsin antagonist, was ineffective in a formal controlled trial in healing duodenal ulcer and in preventing recurrent bleeding in patients admitted with haematemesis and melaena."

8) U.S. 4,101,650 discloses long-acting pepstatin floating minicapsules comprising center particles of sodium bicarbonate coated with a water-soluble film-coating agent, which are further coated with pepstatin and a water-soluble film coating agent. Because of the release of carbon dioxide in gastric juice, these minicapsules float in the stomach and provide pepsin suppression for 3-5 hours as compared with about 1 hour for plain pepstatin.

9) Published United Kingdom Patent Application No. 2,067,987 discloses a large number of the histamine $H_2$-receptor antagonists of Formula I herein which are utilized in the methods and compositions disclosed and claimed in the present invention. However, it does not disclose that such compounds may be administered concomitantly with pepstatin and thereby provide enhanced antiulcer activity.

This invention relates to a pharmaceutical composition comprising a mixture of the pepsin-inhibiting agent, pepstatin, and at least one histamine $H_2$-receptor antagonist of the formula



I

wherein p is 1 or 2;

$R^1$ is hydroxy or $NR^2R^3$;

$R^2$ and $R^3$ each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxy(lower)alkyl, (lower)-alkylthio(lower)alkyl, 2-fluoroethyl, 2,2,2-trifluoroethyl or cyano(lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ may also be cyclo(lower)alkyl, amino(lower)alkyl, (lower)alkylamino(lower)-alkyl, di(lower)alkylamino(lower)alkyl, pyrrolidino(lower)alkyl, piperidino(lower)alkyl, morpholino(lower)alkyl, piperazino(lower)-alkyl, pyridyl(lower)alkyl, substituted pyridyl(lower)alkyl wherein the pyridyl ring may contain one substituent selected from (lower)alkyl, (lower)alkoxy, hydroxy, amino and halogen, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, (lower)-alkoxy, 2,3-dihydroxypropyl, cyano, amidino, (lower)alkylamidino, $A'-(CH_2)_m,Z'(CH_2)_n,-$, phenyl, phenyl(lower)alkyl, substituted phenyl or substituted phenyl(lower)alkyl, wherein the phenyl ring may contain one or two substituents independently selected from

(lower)alkyl, hydroxy, (lower)alkoxy and halogen or one substituent selected from methylenedioxy, trifluoromethyl and di(lower)alkylamino; or $R^2$ and $R^3$, taken together, may be $-CH_2CH_2X(CH_2)_r-$;

r is an integer of from 1 to 3, inclusive;

X is methylene, sulfur, oxygen or $N-R^4$, provided that, when r is 1, X is methylene;

$R^4$ is hydrogen, (lower)alkyl, (lower)alkenyl, (lower)-alkynyl, (lower)alkanoyl or benzoyl;

m and m' each are independently an integer of from zero to 2, inclusive;

n and n' each are independently an integer of from 2 to 4, inclusive;

Z and Z' each are independently sulfur, oxygen or methylene;

A and A' each are independently phenyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, furyl, thienyl or pyridyl; provided that A and A' independently may contain one or two substituents, the first substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl, (lower)alkoxy,

$$-(CH_2)_qN=C\begin{matrix}\diagup NHR^{14}\\ \diagdown NHR^{15}\end{matrix} \quad \text{and} \quad -(CH_2)_qNR^5R^6,$$

and the second substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl and (lower)alkoxy;

q is an integer of from 0 to 6, inclusive; $R^{14}$ and $R^{15}$ independently are hydrogen or (lower)alkyl, or, if $R^{14}$ is hydrogen, $R^{15}$ also may be (lower)alkanoyl or benzoyl, or $R^{14}$ and $R^{15}$, taken together, may be ethylene; and

$R^5$ and $R^6$ each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkoxy(lower)alkyl, cyclo(lower)alkyl, phenyl or phenyl(lower)alkyl, provided that $R^5$ and $R^6$ may not both be cyclo(lower)alkyl or phenyl; or $R^5$ and $R^6$, taken together with the nitrogen atom to which they are

attached, may be pyrrolidino, methylpyrrolidino, dimethylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, dimethylpiperidino, hydroxypiperidino, N-methylpiperazino, homopiperidino, heptamethyleneimino or octamethyleneimino;

or a nontoxic, pharmaceutically acceptable salt, hydrate or solvate thereof.

The method of treating peptic ulcers in a warm-blooded animal in need of such treatment comprises concomitantly administering to said animal a peptic activity-inhibiting amount of pepstatin and an effective antiulcerogenic amount of at least one compound of Formula I, or a pharmaceutically acceptable acid addition salt, hydrate or solvate thereof.

The improvement in the treatment of peptic ulcers in a warm-blooded animal by the administration to said animal of an effective antiulcerogenic amount of at least one compound of Formula I, or a pharmaceutically acceptable acid addition salt, hydrate or solvate thereof, comprises reducing the amount of the compound of Formula I necessary for effective treatment by concomitantly administering to said animal a peptic activity-inhibiting amount of pepstatin.

The compounds of Formula I are not themselves our invention, but are the invention of our colleagues, Aldo A. Algieri and Ronnie R. Crenshaw.

The compounds of Formula I are relatively nontoxic substances, as demonstrated by pharmacological studies in animals of some of the compounds. These studies showed a toxicity profile substantially the same as that of the commercial $H_2$-antagonist cimetidine. Although widespread human usage of cimetidine has demonstrated it to be a relatively safe drug with a low incidence of side-effects, it would, of course, be desirable to even further reduce the side-effect liability of such a drug. Some of the preferred compounds of Formula I have been shown by various animal studies to be up to about 400 times

as potent as cimetidine as inhibitors of gastric secretion, depending on the animal model and route of administration. The preferred compounds of Examples 86 and 88 are about 30 and 15, respectively, times more potent than cimetidine by the oral route. Based on this potency difference, the oral dosage of the compounds of Examples 86 and 88 would be about 1/30 and 1/15, respectively, that of cimetidine, thus reducing the expected incidence of side effects. The usual oral dosage of cimetidine is 300 mg, given four times a day, while the usual dosage of the compounds of Examples 86 and 88 is about 10 mg and 20 mg, respectively, given four times a day. It was an object of this invention to further reduce the necessary dosage of the compounds of Formula I by the concomitant administration of a peptic activity-inhibitory amount of pepstatin. As will be shown below, such concomitant administration provides about a two- to three-fold increase in potency compared with the administration of an equal amount of the compound of Formula I alone, thus permitting a further two- to three-fold reduction in the dosage of the compound of Formula I.

Pepstatin has also been shown by pharmacological studies in animals to be a relatively nontoxic substance; its $LD_{50}$ exceeded 3000 mg/kg in all animal species studied [Svendsen, L. B. et al., Scand. J. Gastroent., 11, 459-463 (1976)]. It is essentially unabsorbed upon oral administration; no side effects were observed in human patients with ulcer dyspepsia receiving daily oral doses of 700 mg of pepstatin for up to three months [Svendsen, L. B. et al. (1976) supra]. Pepstatin does not inhibit the production of pepsin but inhibits peptic activity by forming a 1:1 pepsin-pepstatin complex which is devoid of proteolytic activity.

In patients with ulcer dyspepsia, it has been demonstrated that pepstatin inhibits gastric peptic activity, but has no effect on the gastric acidity [Svendsen, L. B. et al., Scan. J. Gastroent., 11, 459-463 (1976)]. In contrast, the histamine $H_2$-receptor antagonist cimetidine has been shown to antagonize both basal and stimulated gastric acid secretion in normal volunteers [Burland, W. L. et al., Brit. J. Clin. Pharmacol., 2, 481-486 (1975)] and in patients with duodenal

ulcer [Longstreth, G. F. et al., New England J. Med., 294, 801-804 (1976)], but its effect on pepsin secretion is less marked [Binder, H. J. and Donaldson Jr., R. M., Gastroenterology, 74, 371-375 (1978)]. The results of those studies indicate that pepstatin and cimetidine act by different mechanisms. The inhibitory effect of the compounds of Formula I on gastric acid secretion is also significantly greater than on pepsin activity, and in this respect its pharmacological profile is similar to that of cimetidine.

In the tests described below, gastric erosions produced in rats by the oral instillation of 1.0 mL of 0.75N HCl were compared with those in rats which had been pretreated with the most preferred compound of Formula I (of Example 1) or with that compound and pepstatin. Comparison tests utilizing pretreatment with the newer commercial product, ranitidine, and with ranitidine and pepstatin, are also shown. Ranitidine is about 4 and 6 times as potent as cimetidine as an inhibitor of gastric secretion, by the oral route, in the rat and dog, respectively.

## Experimental Methods

A modification of the method of Robert et al., [Gastroenterology, 77, 433-443 (1979)] was employed to produce gastric erosions. Adult male, Long Evans rats weighing 280-300 g (Blue Spruce Farms, Alton, New York) were used. The animals were individually caged and food and water were removed 24 and 18 hours, respectively, prior to testing. On the following day, the test compound was administered orally to the animals 30 minutes before 1.0 mL of 0.75N HCl was instilled into the stomach by gavage. Animals treated with the combination of the test compound and pepstatin received the test compound 30 minutes before, and a fixed amount of pepstatin (20 mg/kg po) 10 minutes before, the hydrochloric acid was administered. Previous studies in our laboratories had shown that this dose of pepstatin (20 mg/kg po) completely inhibited pepsin activity and antagonized ulcer formation in the 18 hour pylorus ligated rat. One hour after receiving the HCl solution, the animals were sacrificed with an intraperitoneal injection of 0.2 mL of T-61®, a euthanasia solution (National Laboratories Corp.).

The stomachs were removed from the animals, cut along the greater curvature, opened, rinsed with saline and pinned out flat in a standard position for macroscopic examination and scoring of erosions. The stomachs were photographed with a Polaroid® Close Up camera (Polaroid Corporation) and scoring was determined from the photographs. For scoring purposes, only those erosions with a minimum length of 1 mm were considered. The severity of gastric ulceration was defined for each animal as the sum of the maximum continuous lengths (in mm) of the erosions satisfying the above criteria. Percent inhibition of lesion formation was defined as

$$\frac{\text{(mm erosion, vehicle control) - (mm erosion, test agent)}}{\text{(mm erosion, vehicle control)}} \times 100.$$

Data were analyzed using the t-test for unpaired data and $ED_{50}$ values were calculated from the dose response data using probit analysis [Finney, Probit Analysis, 3rd ed., University Press, Cambridge, England (1971)].

The compound of Example 1 and ranitidine (synthesized by the Medicinal Chemistry Research Department of Bristol Laboratories, Division of Bristol-Myers Company) were dissolved in one equivalent of HCl and the pH adjusted to 5.5 with NaOH. A suspension of pepstatin (Banyu Pharmaceutical Co. Ltd.) in water was made by homogenizing the compound with a few drops of Tween-80® (Atlas Chemical Industries). Each of these compounds were administered orally by gavage in a volume of 2 mL/kg.

## Test Results

The instillation of HCl to untreated rats caused extensive gastric erosions consisting of elongated bands 1-10 mm long by 1-3 mm wide. These erosions were located primarily in the corpus (portion of the stomach which secretes acid and pepsin), while the antrum was not as severely affected and no lesions were observed in the forestomach (the non-secretory portion). These findings are similar to those reported by Robert et al., in their initial description of this procedure.

Pretreatment of the rats with 25, 50 or 75 mg/kg of the compound of Example 86 prior to instillation of the HCl decreased the formation of gastric erosions in a dose-related manner. Pretreatment of the rats with the above amounts of the compound of Example 86 plus 20 mg/kg of pepstatin significantly enhanced the inhibitory effect of the compound of Example 86 when the latter was given at 25 mg/kg. An enhancement was also seen at 50 mg/kg, but the significance level was between .05 and .10. A small, non-significant enhancement was observed at 75 mg/kg. Figure 1 shows, in graphic form, the percent of reduction in gastric erosions over that of the control rats (no pretreatment) which was obtained at each of the dosage levels of the compound of Example 86 alone and with pepstatin. When the data shown in Figure 1 were analyzed by probit analysis according to Finney, it was shown that the response to the compound of Example 86 was linear with respect to the log of the dose administered and that the addition of pepstatin shifted the dose response to the left in a parallel manner. These data are shown in Figure 2. It may be seen from Figure 2 that the $ED_{50}$ values for the compound of Example 86 alone and with pepstatin were found to be 82 and 46 mg/kg, respectively, thus showing that the combination had approximately twice the potency of the compound of Example 86 alone.

Pretreatment of the rats with a 25, 50, 100 or 200 mg/kg dose of the compound of Example 88 prior to instillation of the HCl also decreased the formation of gastric erosions in a dose-related manner. Pretreatment of rats with the above amounts of the compound of Example 88 plus 20 mg/kg of pepstatin significantly enhanced the inhibitory effect of the compound of Example 88 when the latter was dosed at 25 or 50 mg/kg. No further enhancement of the inhibitory effect over that of the compound of Example 88 alone occurred when pepstatin and 100 mg/kg or 200 mg/kg of the compound of Example 88 were used for pretreatment. Figure 3 shows, in graphic form, the percent of reduction in gastric erosions over that of the control rats (no pretreatment) which was obtained at each of the dosage levels of the compound of Example 88 alone and with pepstatin. When the

data shown in Figure 3 were analyzed by probit analysis according to Finney, it was shown that the response to the compound of Example 88 was linear with respect to the log of the dose administered. Furthermore, with concomitant administration of pepstatin, the response was also linear with respect to the log dose of the compound of Example 88, but the two lines were not parallel. These data are shown in Figure 4. It may be seen from Figure 4 that the $ED_{50}$ values for the compound of Example 88 alone and with pepstatin were found to be 63 and 25 mg/kg, respectively. At the $ED_{50}$ level, the combination was 2.5 times as potent as the compound of Example 88 alone.

Pretreatment of rats with a 25, 50, 75 or 100 mg/kg dose of ranitidine prior to instillation of the HCl similarly decreased the formation of gastric erosions in a dose-related manner. No enhancement of the inhibitory effect over that of ranitidine alone occurred when pepstatin was given along with ranitidine. Figure 5 shows, in graphic form, the percent reduction in gastric erosions over that of the control rats (no pretreatment), which was obtained at each of the dosage levels of ranitidine alone and ranitidine plus pepstatin. When the data shown in Figure 5 were analyzed by probit analysis according to Finney, it was shown that the response to ranitidine was linear with respect to the log dose of the compound and that the addition of pepstatin shifted the dose response to the left in a parallel manner. These data are shown in Figure 6. It may be seen from Figure 6 that the $ED_{50}$ values for ranitidine alone and the ranitidine-pepstatin combination were found to be 123 and 104 mg/kg, respectively. The ratio of potencies of the combination to ranitidine alone was 1.18, which was not statistically different from unity.

The data from these tests are summarized in Table 1. It may be seen that the $ED_{50}$'s for the compounds of Examples 86 and 88, given alone, were about 1.5 and 2 times, respectively, more potent than ranitidine given alone. When each of these compounds were administered with pepstatin, the compounds of Examples 86 and 88 were about 2.3 and 4.2 times, respectively,

more potent than ranitidine plus pepstatin.

Table 1

Comparison of the Compound of Example 1 and Ranitidine in Inhibiting HCl-Induced Formation of Gastric Lesions, Alone or in Combination with Pepstatin

| Compound | $ED_{50}$ (mg/kg) for Inhibition of Ulcer Formation | | |
|---|---|---|---|
| | Alone | with Pepstatin | Potency Ratio[a] |
| Compound of Example 88 | 63 | 25 | 2.5[b] |
| Compound of Example 86 | 82 | 46 | 1.8 |
| Ranitidine | 123 | 104 | 1.18 |

[a]Ratio of potency (cpd. alone) to potency of combination (cpd. plus pepstatin).

[b]Defined as ratio of $ED_{50}$ (cpd. of Example 88 alone) to $ED_{50}$ (cpd. of Example 88 plus pepstatin); dose-response lines were nonparallel.

Antagonism of $H_2$-receptors and the subsequent antisecretory effect probably is not the mechanism of the antiulcer effect in this test, since exogenous HCl is being supplied. Pepstatin is only poorly absorbed following oral administration as animal studies have shown that more than 90 percent of the compound is excreted in the feces within 72 hours. Therefore, the inhibition of proteolytic activity following oral administration of pepstatin is due primarily to a local effect of this compound.

In order to obtain the maximum benefit of the present invention, it is desirable that the dosage of pepstatin be such that there is substantially complete inhibition of gastric pepsin activity for as long a period of the day as practical. When

pepstatin was administered to ulcer patients in 100 mg doses seven times a day (with meals, two hours after meals and at bedtime), pepsin activity was inhibited for 18 hours a day.

In one preferred embodiment of this invention, pepstatin is administered in dosages of about 100 mg seven times a day. In another preferred embodiment of this invention, pepstatin is administered in dosages of about 175 mg four times a day. In a more preferred embodiment of this invention the pepstatin is administered in the form of floating minicapsules as described in U.S. Patent 4,101,650. The pepstatin floating minicapsules provide pepsin suppression for about 3-5 times as long as plain pepstatin and, in this form, may be administered, for example, four times a day in a dosage of floating minicapsules containing about 100 mg of pepstatin.

The dosage of the compounds of Formula I to be administered concomitantly with pepstatin will depend not only on such factors as the weight of the patient, but also on the degree of gastric acid inhibition desired and the potency of the particular compound being utilized. The decision as to the particular dosage to be employed is within the discretion of the physician. In the Heidenhain Pouch Dog test described below, cimetidine has an oral $ED_{50}$ of approximately 3.3 μmoles/kg. The usual human adult oral dose of cimetidine is 300 mg, given four times a day. The usual human adult starting oral dosages of the compounds of Formula I (without pepstatin) are readily determined from their oral $ED_{50}$ in this same test. Thus, if the oral $ED_{50}$ of a particular compound of Formula I is 0.33 μmoles/kg, the usual starting dosage (without pepstatin) would be approximately 30 mg, given four times a day, etc. When administered concomitantly with pepstatin, the usual starting dose would be approximately 15 mg, given four times a day. Similar calculations may be made for parenteral dosages. These starting dosages (and the number of times administered per day) may, of course, be varied by titration of the dosage to the particular circumstances of the specific patient.

It will be appreciated by those skilled in the art that, to obtain the benefits of the present invention, it is not necessary to physically combine the compound of Formula I and pepstatin in a single unitary dosage form. Not only may the two active ingredients be taken separately, but they may even be given by different routes of administration. Although pepstatin provides its effects by local action in the stomach and must be given orally, the compound of Formula I may be given orally or parenterally. For convenience, however, it usually is preferred to administer it orally.

The treatment of peptic ulcers in a warm-blooded animal in need of such treatment comprises concomitantly administering to said animal a peptic activity-inhibiting amount of pepstatin and an effective antiulcerogenic amount of at least one compound of Formula I, or a pharmaceutically acceptable acid addition salt, hydrate or solvate thereof. In man, the usual dosage of the preferred compounds of Formula I is from about 2 to about 100 mg (and most preferably from about 4 to about 50 mg), given three or four times (and most preferably four times) a day. With particularly preferred compounds of Formula I, the usual dosage is from about 2 to about 50 mg, and preferably from about 4 to about 25 mg. The preferred dosage of pepstatin in man is from about 100 mg when administered about seven times a day, to about 175 mg when administered about four times a day. However, in a more preferred embodiment of this invention, when the pepstatin is in the form of pepstatin floating minicapsules, the preferred dosage is that amount of minicapsules containing about 100 mg of pepstatin, administered about four times a day.

The improvement in the treatment of peptic ulcers in a warm-blooded animal by administering to said animal an effective antiulcerogenic amount of at least one compound of Formula I or a pharmaceutically acceptable acid addition salt, hydrate or solvate thereof, comprises reducing the amount of the compound of Formula I necessary for effective treatment by

concomitantly administering a peptic activity-inhibiting amount of pepstatin. The preferred dosage of pepstatin and of pepstatin floating minicapsules in man is as described in the preceding paragraph.

There is provided by the present invention a pharmaceutical composition useful in the treatment of peptic ulcers, which comprises a peptic activity-inhibiting amount of pepstatin and an effective antiulcerogenic amount of at least one compound of Formula I, or a pharmaceutically acceptable acid addition salt, hydrate or solvate thereof, and a pharmaceutically acceptable carrier. In a preferred embodiment the composition contains from about 2 to about 100 mg (and most preferably from about 4 to about 50 mg) of one of the preferred compounds of Formula I and from about 100 to about 175 mg of pepstatin. In particularly preferred embodiments, the composition contains from about 2 to about 50 (and most preferably from about 4 to about 25) mg of the compound of Example 1, plus from about 100 to about 175 mg of pepstatin. Preferably the compositions according to the invention are in unitary dosage form.

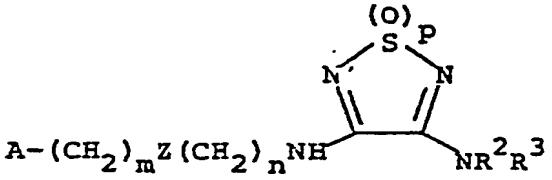
As used herein, reference to a pharmaceutically acceptable acid addition salt of a compound of Formula I means the mono- or di-salt with a nontoxic pharmaceutically acceptable organic or inorganic acid. Such acids are well known and include hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, maleic, fumaric, succinic, oxalic, benzoic, methanesulfonic, ethanedisulfonic, benzenesulfonic, acetic, propionic, tartaric, citric, camphorsulfonic, levulinic and the like. The salts are made by methods known in the art.

The present invention includes within its scope the use of all possible tautomeric forms, geometric isomers, optical isomers and zwitterionic forms of the compounds of Formula I, as well as mixtures thereof. As used herein and in the claims, the terms "(lower)alkyl," "(lower)alkenyl," "(lower)alkynyl," "(lower)-alkoxy" and "(lower)alkylthio" mean, in their broadest sense,

straight or branched chain alkyl, alkenyl, alkynyl, alkoxy and alkylthio groups containing from 1 to 12 carbon atoms. Preferably, these groups contain from 1 to 8 carbon atoms and, most preferably, from 1 to 6 carbon atoms.

In practicing the present invention, a wide variety of pharmaceutical forms may be employed for the administration of the compound of Formula I and pepstatin, or the pharmaceutical composition containing both entities. Thus, if a solid carrier is used, the preparations may be tableted, placed in a hard gelatin capsule in powder or pellet form, or in the form of a troche or lozenge. If a liquid carrier is used, the preparations may be in the form of a soft gelatin capsule, syrup, emulsion, aqueous or non-aqueous suspension or, in the case of the compounds of Formula I, a sterile solution or suspension for injection. These pharmaceutical dosage forms are prepared by conventional techniques.

In a preferred embodiment of the invention the compounds of Formula I have the structure



Id

wherein p is 1 or 2;

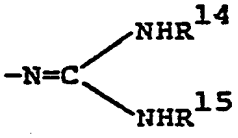
$R^2$ and $R^3$ each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl or cyclo(lower)alkyl(lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ also may be pyridyl(lower)alkyl, substituted pyridyl(lower)alkyl wherein the pyridyl ring may contain one substituent selected from (lower)alkyl, (lower)alkoxy, hydroxy, amino and halogen, $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$, phenyl(lower)-alkyl or 3,4-methylenedioxybenzyl;

m and m' each are independently zero or 1;

n and n' each are independently 2 or 3;

Z and Z' each are independently sulfur, oxygen or methylene;

A and A' each are independently phenyl, imidazolyl, thiazolyl, furyl, thienyl or pyridyl; provided that A and A' independently may contain one or two substituents, the first substituent being selected from (lower)alkyl,



and $-CH_2NR^5R^6$,

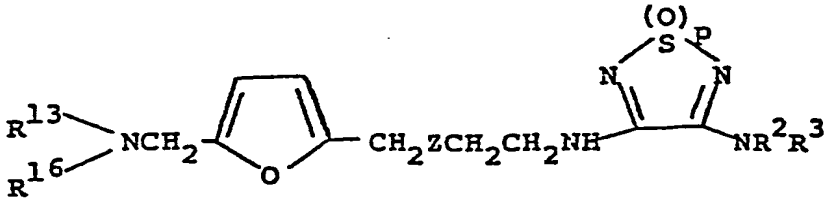
and the second substituent being selected from (lower)alkyl;

$R^{14}$ and $R^{15}$ independently are hydrogen or (lower)alkyl, or $R^{14}$ and $R^{15}$, taken together, may be ethylene; and

$R^5$ and $R^6$ each are independently hydrogen or (lower)-alkyl; or $R^5$ and $R^6$, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, dimethylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, dimethylpiperidino, hydroxypiperidino, N-methylpiperazino, homopiperidino, heptamethyleneimino or octamethyleneimino;

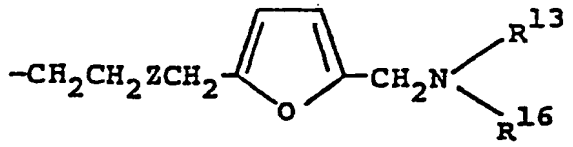
or a nontoxic, pharmaceutically acceptable salt, hydrate or solvate thereof.

In another preferred embodiment of the invention the compounds of Formula I have the structure



Ie

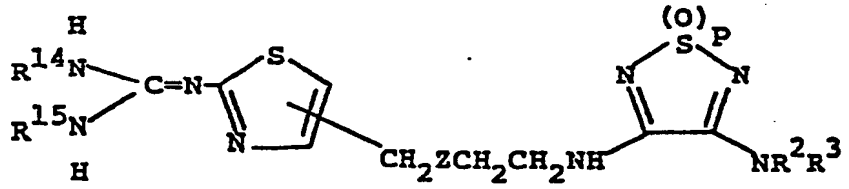
wherein p is 1 or 2; Z is sulfur or methylene; $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ also may be (lower)alkenyl, (lower)alkynyl, phenyl(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, pyridylmethyl or



;

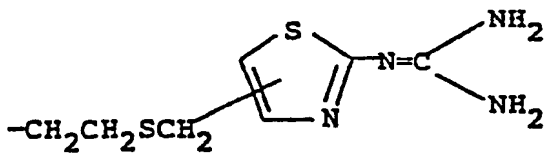
$R^{16}$ is methyl and $R^{13}$ is hydrogen or methyl, or $R^{16}$ and $R^{13}$, taken together with the nitrogen atom to which they are attached, may be piperidino; or a nontoxic pharmaceutically acceptable salt, hydrate or solvate thereof.

In another preferred embodiment of the invention the compounds of Formula I have the structure

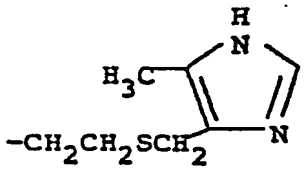


If

wherein p is 1 or 2; Z is sulfur or methylene; $R^{14}$ and $R^{15}$ independently are hydrogen or methyl, or, $R^{14}$ and $R^{15}$, taken together, may be ethylene; and $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ also may be (lower)alkenyl, (lower)alkynyl, pyridylmethyl,



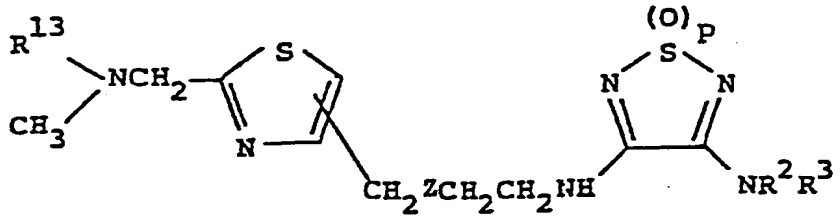
or



;

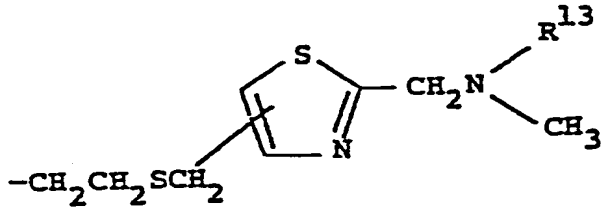
or a nontoxic pharmaceutically acceptable salt, hydrate or solvate thereof.

In another preferred embodiment of the invention the compounds of Formula I have the structure



Ig

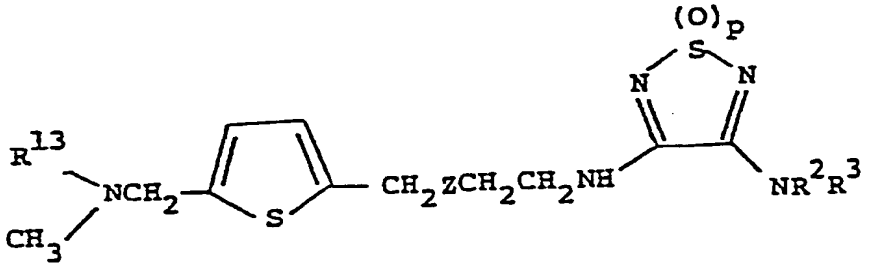
wherein p is 1 or 2; Z is sulfur or methylene; $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or when $R^2$ is hydrogen, $R^3$ also may be (lower)alkenyl, (lower)-alkynyl or



;

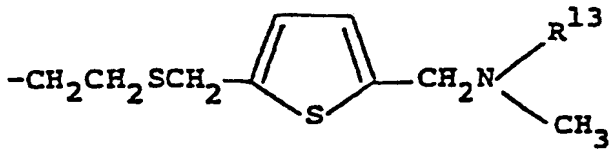
and $R^{13}$ is hydrogen or methyl; or a nontoxic pharmaceutically acceptable salt, hydrate or solvate thereof.

In another preferred embodiment of the invention the compounds of Formula I have the structure



Ih

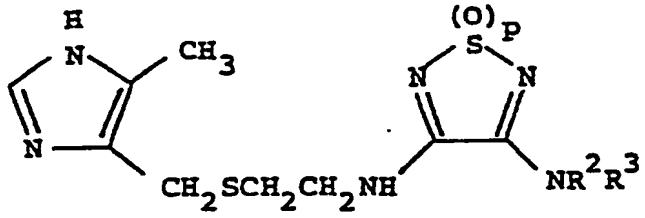
wherein p is 1 or 2; Z is sulfur or methylene; $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ also may be (lower)alkenyl, (lower)-alkynyl, phenyl(lower)alkyl, pyridylmethyl, 3,4-methylenedioxybenzyl or



;

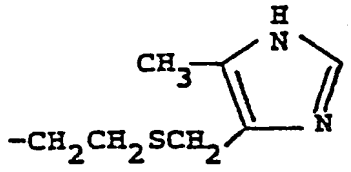
and $R^{13}$ is hydrogen or methyl; or a nontoxic pharmaceutically acceptable salt, hydrate or solvate thereof.

In another preferred embodiment of the invention the compounds of Formula I have the structure



Ii

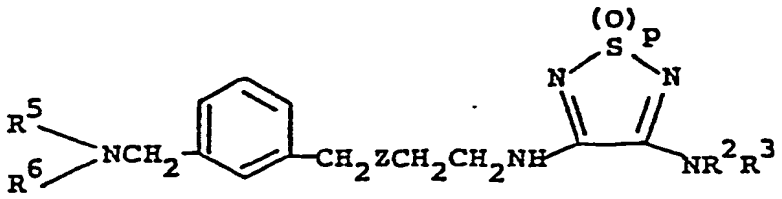
wherein p is 1 or 2; and $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ also may be (lower)alkenyl, (lower)alkynyl or



;

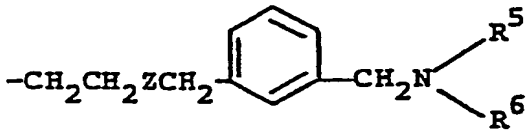
or a nontoxic pharmaceutically acceptable salt, hydrate, or solvate thereof.

In another preferred embodiment of the invention the compounds of Formula I have the structure



Ij

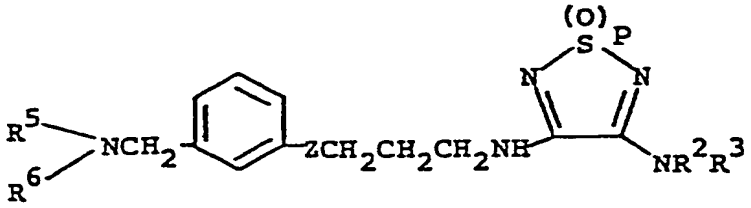
wherein p is 1 or 2; Z is sulfur or methylene; $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ also may be (lower)alkenyl, (lower)alkynyl or



;

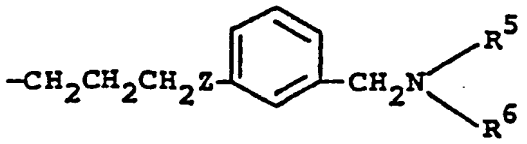
and $R^5$ and $R^6$ each are independently hydrogen or (lower)alkyl, or, $R^5$ and $R^6$, taken together with the nitrogen atom to which they are attached, may be piperidino; or a nontoxic, pharmaceutically acceptable salt, hydrate or solvate thereof.

In another preferred embodiment of the invention the compounds of Formula I have the structure



Ik

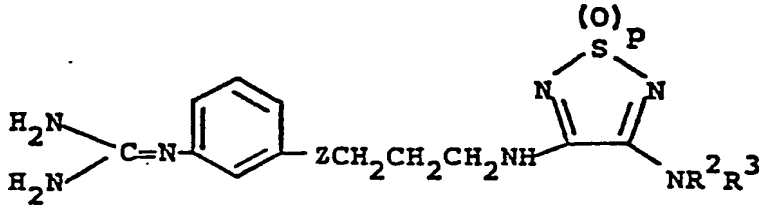
wherein p is 1 or 2; Z is oxygen or sulfur; $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ also may be (lower)alkenyl, (lower)alkynyl, pyridylmethyl or



;

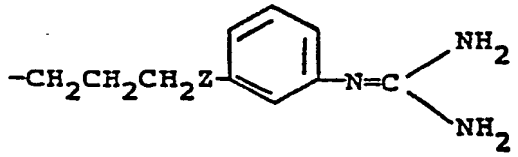
and $R^5$ and $R^6$ each are independently hydrogen or (lower)alkyl, or, when $R^5$ is hydrogen, $R^6$ also may be (lower)alkenyl or (lower)alkynyl; or $R^5$ and $R^6$, taken together with the nitrogen to which they are attached, may be pyrrolidino, methylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, dimethylpiperidino, homopiperidino or heptamethyleneimino; or a nontoxic pharmaceutically acceptable salt, hydrate or solvate thereof.

In another preferred embodiment of the invention the compounds of Formula I have the structure



II

wherein p is 1 or 2; Z is oxygen or sulfur; $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ may be (lower)alkenyl, (lower)alkynyl, pyridylmethyl or



or a nontoxic pharmaceutically acceptable salt, hydrate or solvate thereof.

As presently envisaged, the particularly preferred compounds of Formula I utilized in this invention are

a) 3-{2-[(5-Dimethylaminomethyl-2-furyl)-methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,

b) 3-{2-[(5-Dimethylaminomethyl-2-furyl)-methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide,

c) 3-{2-[(5-Dimethylaminomethyl-2-furyl)-methylthio]ethylamino}-4-ethylamino-1,2,5-thiadiazole 1-1-dioxide,

d) 3-{2-[(5-Dimethylaminomethyl-2-furyl)-methylthio]ethylamino}-4-(n-propyl)amino-1,2,5-thiadiazole 1,1-dioxide,

e) 3-Allylamino-4-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide,

f) 3-{2-[(5-Dimethylaminomethyl-2-furyl)methyl-thio]ethylamino}-4-(2-propynyl)amino-1,2,5-thiadiazole 1,1-dioxide,

g) 3-{2-[(5-Dimethylaminomethyl-2-furyl)methyl-thio]ethylamino}-4-amino-1,2,5-thiadiazole 1,1-dioxide,

h) 3-{2-[(5-Dimethylaminomethyl-2-furyl)methyl-thio]ethylamino}-4-amino-1,2,5-thiadiazole 1-oxide,

i) 3-Amino-4-[3-(3-pyrrolidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,

j) 3-{4-(5-Dimethylamino-2-furyl)butylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,

k) 3-Methylamino-4-[3-(3-pyrrolidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,

l) 3-{2-[(2-Guanidinothiazol-4-yl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,

m) 3-{2-[(2-Guanidinothiazol-4-yl)methylthio]-ethylamino}-4-(2-propynyl)amino-1,2,5-thiadiazole 1,1-dioxide,

n) 3-Amino-4-[3-(3-pyrrolidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide,

o) 3-{2-[(2-Guanidinothiazol-4-yl)methylthio]-ethylamino}-4-amino-1,2,5-thiadiazole 1,1-dioxide,

p) 3-{2-[(2-Dimethylaminomethyl-4-thiazolyl)-methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,

q) 3-{2-[(5-Dimethylaminomethyl-2-thienyl)-methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,

r) 3-{2-[(5-Dimethylaminomethyl-2-furyl)-methylthio]ethylamino}-4-ethylamino-1,2,5-thiadiazole 1-oxide,

s) 3-Amino-4-{3-[3-(4-methylpiperidinomethyl)-phenoxy]propylamino}-1,2,5-thiadiazole 1,1-dioxide,

t) 3-Amino-4-{2-[(2-guanidinothiazol-4-yl)methylthio]-ethylamino}-1,2,5-thiadiazole 1-oxide,

u) 3-Benzylamino-4-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide,

v) 3-{2-[(3-{Dimethylaminomethyl}phenyl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,

w) 3-Amino-4-{2-[(3-{dimethylaminomethyl}phenyl)-methylthio]ethylamino}-1,2,5-thiadiazole 1-oxide,

x) 3-{2-[(5-Dimethylaminomethyl-2-thienyl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide,

y) 3-Amino-4-{4-(5-dimethylaminomethyl-2-furyl)-butylamino}-1,2,5-thiadiazole 1,1-dioxide,

z) 3-Amino-4-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide,

aa) 3-Butylamino-4-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide,

bb) 3-Cyclopropylmethylamino-4-{2-[(5-dimethylamino-methyl-2-furyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide,

cc) 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]-ethylamino}-4-[(2-pyridyl)methylamino]-1,2,5-thiadiazole 1,1-dioxide,

dd) 3-Amino-4-{3-[3-(4-methylpiperidinomethyl)-phenoxy]propylamino}-1,2,5-thiadiazole 1-oxide,

ee) 4-{2-[(5-Dimethylaminomethyl-2-thienyl)-methylthio]ethylamino}-3-(1-propylamino)-1,2,5-thiadiazole 1,1-dioxide,

ff) 3-{2-[(2-Guanidinothiazol-4-yl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide,

gg) 3-{3-[3-(hexamethyleneiminomethyl)phenoxy]-propylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,

hh) 3-[3-(3-dimethylaminomethylphenoxy)propylamino]-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,

ii) 3-Amino-4-{3-[3-(hexamethyleneiminomethyl)-phenoxy]propylamino}-1,2,5-thiadiazole 1-oxide,

jj) 4-{2-[(5-Dimethylaminomethyl-2-thienyl)-methylthio]ethylamino}-3-(3-pyridyl)methylamino-1,2,5-thiadiazole 1,1-dioxide,

kk) 3-Amino-4-[3-(3-morpholinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,

ll) 3-Methylamino-4-[3-(3-morpholinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,

mm) 3-Amino-4-[3-(3-dimethylaminomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide,

nn) 3-Amino-4-{3-[3-(heptamethyleneiminomethyl)-phenoxy]propylamino}-1,2,5-thiadiazole 1-oxide,

oo) 3-[(3-Pyridyl)methylamino]-4-[3-(3-piperidino-methylphenoxy)propylamino]-1,2,5-thiadiazole 1-oxide,

pp) 3-Amino-4-{2-[(2-{2-methylguanidino}thiazol-4-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1-oxide,

qq) 3-Methylamino-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,

rr) 3-Amino-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide,

ss) 3-{2-[(5-Dimethylaminomethyl-2-thienyl)-methylthio]ethylamino}-4-ethylamino-1,2,5-thiadiazole 1,1-dioxide,

tt) 3-Amino-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,

uu) 3-Amino-4-[3-(3-guanidinophenoxy)propylamino]-1,2,5-thiadiazole 1-oxide.

Histamine $H_2$-receptor antagonists have been shown to be effective inhibitors of gastric secretion in animals, including man, Brimblecombe et al., J. Int. Med. Res., 3, 86 (1975). Clinical evaluation of the histamine $H_2$-receptor antagonist cimetidine has shown it to be an effective therapeutic agent in the treatment of peptic ulcer disease, Gray et al., Lancet, 1, 8001 (1977). Two of the standard animal models for determining gastric antisecretory activity of histamine $H_2$-antagonists are the Gastric Fistula Rat and the Heidenhain Pouch Dog. The $ED_{50}$'s for some of the compounds of Formula I in these two animal models are given in Tables 2 and 3, below.

Determination of Gastric Antisecretory Activity in the Gastric Fistula Rat

Male Long Evans rats weighing about 240-260 grams at the time of cannula implantation are used. The design and implantation of the stainless steel cannula into the anterior wall of the fore-stomach are carried out essentially as described by Pare et al. [Laboratory Animal Science, 27, 244 (1977)]. The fistula components are designed and the operative procedure is carried out exactly as described in the above reference. Post operatively the animals are individually housed in solid bottom cages with sawdust and are allowed food and water ad libitum throughout the entire recovery period. Animals are not used for test purposes for at least 15 days after the operative procedure.

The animals are fasted but allowed water ad libitum for 20 hours before the testing procedure is to begin. Immediately prior to collection, the cannula is opened and the stomach washed gently with 30-40 mL of warm saline or distilled

water to remove any residual contents. The catheter is then screwed into the cannula in place of the plugging screw and the rat is placed in a clear plastic rectangular cage measuring 40 cm long, 15 cm wide and 13 cm high. The bottom of the cage has a slit approximately 1.5 cm wide and 25 cm long running down the center to accommodate the catheter which hangs through it. In this way the rat is not restricted and can move freely about the cage during collection periods. The remainder of the assay is carried out as described by Ridley et al. [Research Comm. Chem. Path. Pharm., 17, 365 (1977)].

Gastric secretions collected during the first hour after washing the stomach are discarded as they may be contaminated. For oral evaluation, the catheter is then removed from the cannula and replaced with the plugging screw. Water (2 mL/kg) is administered orally via gastric intubation and the animal is returned to the cage for 45 minutes. After this time the plugging screw is removed and replaced with a catheter to which a small plastic vial has been attached to collect the gastric secretions. A two hour sample is collected (this represents the control secretion); the catheter removed and replaced with the plugging screw. The test drug is now administered orally in a volume of 2 mL/kg via gastric intubation. Forty-five minutes later the plugging screw is again removed, replaced with the catheter attached to a small plastic vial and another 2 hour sample is collected. The secretions in the second sample are compared to those of the control sample in order to determine the effects of the test drug.

When test compounds are to be evaluated parenterally, the animal is injected ip or sc with the test compound vehicle in a volume of 2 mL/kg immediately after discarding the initial 60 minute collection. A two hour sample is collected (control secretion) and the animals are injected either ip or sc with the test compound in a volume of 2 mL/kg. An additional two hour sample is collected and its secretions are compared to those of the control period to determing drug effects.

The samples are centrifuged in a graduated tube for volume determination. Titratable acidity is measured by titrating a one mL sample to pH 7.0 with 0.02N NaOH, using an Autoburet and an electrometric pH meter (Radiometer). Titratable acid output is calculated in microequivalents by multiplying the volume in milliliters by the acid concentration in milliequivalents per liter.

Results are expressed as percent inhibition relative to control readings. Dose response curves are constructed and $ED_{50}$ values are calculated by regression analyses. At least three rats are used at each dosage level and a minimum of three dosage levels are utilized for determination of a dose response curve.

## Determination of Gastric Antisecretory Actitity in the Heidenhain Pouch Dog

Prior to surgery, hematology and blood chemistry profiles are obtained and an assessment made as to the general health of selected female dogs. Dogs are vaccinated with Tissue Vax 5 (DHLP - Pitman-Moore) and housed in general animal quarters for four weeks' observation so incipient diseases may become apparent. Dogs are fasted with water ad libitum 24 hours prior to surgery.

Anesthesia is induced with Sodium Pentothal (Abbott) 25-30 mg/kg iv. Subsequent anesthesia is maintained with methoxyflurane (Pitman-Moore). A mid-line linea alba incision from xiphoid to umbilicus provides good exposure and ease of closure. The stomach is pulled up into the operative field, the greater curvature stretched out at multiple points and clamps placed along the selected line of incision. The pouch is made from the corpus of the stomach so that true parietal cell juice is obtained. About 30% of the corpus volume is resected. The cannula is made of light-weight, biologically-inert material such as nylon or Delrin with dimensions and attachments after DeVito and Harkins [J. Appl. Physiol., 14, 138 (1959)]. Post operatively,

dogs are medicated with antibiotics and an analgesic. They are allowed 2-3 months for recovery. Experiments are carried out in the following way: Dogs are fasted overnight (~18 hours) with water ad libitum prior to each experiment. The dogs are placed in a sling and a saphenous vein cannulated for drug administration. Histamine as the base (100 µg/kg/hr) and chlorpheniramine maleate (0.25 mg/kg/hr) are infused continuously (in a volume of 6 mL/hr) with a Harvard infusion pump.

Ninety minutes' infusion are allowed for the dogs to reach a steady state of acid output. At this time the drug or normal saline (control) is administered concomitantly with the secretagogue in a volume of 0.5 mL/kg over a 30 second period. When oral studies are to be carried out, the drug is administered via gastric gavage in a volume of 5 mL/kg. Infusion of the secretagogue is continued and 15 minute samples of the gastric juice are taken for 4.5 hours. Each sample is measured to the nearest 0.5 mL and titratable acidity is determined by titrating a 1 mL sample to pH 7.0 with 0.2N NaOH, using an Autoburet and an electrometric pH meter (Radiometer). Titratable acid output is calculated in microequivalents by multiplying the volume in milliliters by the acid concentration in milliequivalents per liter.

Results are expressed as percent inhibition relative to control readings. Dose response curves are constructed and $ED_{50}$ values are calculated by regression analyses. From 3 to 5 dogs are used at each dose level and a minimum of three dosage levels are utilized for determination of a dose response curve.

Table 2

Effect of Compounds of Formula I on Gastric Acid Output in the Two-Hour Pylorus Ligated Rat

| Compound of Example No. | Route of Administration | $ED_{50}$ * µmoles/kg |
|---|---|---|
| 1 | i.p. | 12.5 (4.90-33.0) |
| 2 | s.c. | ∿100 |
| 3 | i.p. | 0.46 (0.26-0.74) |
| 7 | i.p. | 31.1 (11.1-82.8) |
| 11 B | i.p. | 0.69 (0.31-1.33) |
| 11 C | s.c. | 0.20 (0.03-2.9) |
| 12 | i.p. | 0.28 (0.11-0.69) |
| 13 | s.c. | 0.46 (0.02-3.1) |
| 14 | s.c. | ∿25 |
| 17 | s.c. | 33 (8.7-141) |
| 18 | s.c. | 0.38 (0.02-5.33) |
| 19 | s.c. | 0.34 (0.15-0.81) |
| 20 A | s.c. | 1.15 (0.32-3.7) |
| 21 | s.c. | 0.30 (0.09-1.0) |
| 28 | s.c. | 1.39 (0.39-4.91) |
| 31 | i.p. | 0.41 (0.19-0.81) |
| 32 | i.p. | 0.08 (0.03-0.15) |
| 33 | s.c. | 0.57 (0.16-1.84) |
| 35 | s.c. | 0.08 (0.02-0.22) |
| 36 | s.c. | 1.59 (0.48-6.46) |
| 51 | s.c. | 55 (8.8-930) |
| 52 | s.c. | ∿350 |
| 65 | s.c. | 0.07 (0.02-0.32) |
| 84 | s.c. | 0.15 (0.02-0.53) |
| 85 | s.c. | 0.14 (0.05-0.41) |
| 86 | s.c. | 0.04 (0.015-0.12) |
| 87 | s.c. | 0.02 (0.006-0.04) |
| 88 | s.c. | 0.08 (0.04-0.22) |
| 89 | s.c. | 0.25 (0.07-0.84) |

Table 2 (cont.)

| | | |
|---|---|---|
| 90 | s.c. | 0.86 (0.24-2.69) |
| 91 | s.c. | 1.3 (0.36-3.9) |
| 92 | s.c. | 0.24 (0.09-0.71) |
| 93 | s.c. | 0.14 (0.07-0.32) |
| 94 | s.c. | 0.44 (0.08-1.9) |
| 95 | s.c. | ∿15 |
| 96 | s.c. | ∿15 |
| 97 | s.c. | ∿3 |
| 98 | s.c. | 0.52 (0.08-2.33) |
| 99 | s.c. | 32 (5.7-200) |
| 100 | s.c. | 1.6 (0.38-5.5) |
| 101 | s.c. | 68 (10-750) |
| 102 | s.c. | ∿15 |
| 103 | s.c. | 0.54 (0.21-1.4) |
| 104 | s.c. | 0.61 (0.15-1.88) |
| 105 | s.c. | 1.65 (0.45-4.45) |
| 106 | s.c. | ∿80 |
| 107 | s.c. | 23 (5.1-110) |
| 108 | s.c. | 2.2 (0.54-8.9) |
| 109 | s.c. | 1.4 (0.51-3.9) |
| 110 | s.c. | 0.05 (0.03-0.14) |
| 111 | s.c. | 0.64 (0.17-2.5) |
| 112 | s.c. | 1.2 (0.47-2.9) |
| 113 | s.c. | 0.07 (0.03-0.14) |
| 114 | s.c. | ∿15 |
| 115 | s.c. | 0.57 (0.20-1.6) |
| 116 | s.c. | >10 |
| 117 | s.c. | ∿0.5 |
| 118 | s.c. | 0.066 (0.018-0.19) |
| 119 | s.c. | >10 |
| 120 | s.c. | ∿5 |
| 121 | s.c. | 0.19 (0.055-0.56) |
| 122 | s.c. | ∿10.0 |
| 123 | s.c. | >10 |
| 124 | s.c. | >10 |

Table 2 (cont.)

| | | |
|---|---|---|
| 125 | s.c. | ∿10 |
| 127 | s.c. | >10 |
| 128 | s.c. | ∿10 |
| 129 | s.c. | ∿1 |
| 130 | s.c. | 2.3 (0.79-14) |
| 131 | s.c. | ∿0.5 |
| 132 | s.c. | 0.025 (0.007-0.069) |
| 133 | s.c. | 0.061 (0.019-0.24) |
| 134 | s.c. | 0.024 (0.011-0.050) |
| 135 | s.c. | 0.57 (0.29-1.12) |
| 144 a | s.c. | 0.095 (0.033-0.30) |
| 144 b | s.c. | 0.025 (0.0087-0.065) |
| 144 c | s.c. | 0.14 (0.034-0.44) |
| 144 d | s.c. | 0.91 (0.36-3.2) |
| 145 a | s.c. | 0.056 (0.021-0.18) |
| 145 b | s.c. | ∿0.06 |
| 145 c | s.c. | 0.025 (0.0098-0.057) |
| 145 d | s.c. | 0.05 (0.005-0.2) |
| 146 a | s.c. | 0.023 (0.0091-0.046) |
| 146 d | s.c. | 0.28 (0.066-1.21) |
| 149 | s.c. | ∿0.08 |
| 151 | s.c. | 0.9 (0.15-3.5) |

*Numbers in parentheses are the 95% confidence limits.

Table 3

Oral Gastric Antisecretory Activity of Compounds of Formula I in the Heidenhain Pouch Dog

| Compound of Example | Potency Ratio (cimetidine = 1.0) |
|---|---|
| 11 B | 11 |
| 12 | 10 |
| 18 | 18 |
| 31 | 13 |
| 35 | 20 |
| 65 | 10 |
| 86 | 33 |
| 87 | ∿30 |
| 88 | 13 |
| 118 | 10 |
| 133 | ∿10 |
| 145 c | 8 |
| 146 a | ∿20 |
| 149 | 10 |

As used herein and in the claims, the terms "(lower)-alkyl" and "(lower)alkoxy" mean straight or branched chain alkyl or alkoxy groups containing from 1 to 6 carbon atoms. Preferably these groups contain from 1 to 4 carbon atoms and, most preferably, they contain 1 or 2 carbon atoms. The term "cyclo(lower)-alkyl", as used herein and in the claims, means a cycloalkyl ring containing from 3 to 7 carbon atoms and preferably from 3 to 6

carbon atoms.

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In the following examples, all temperatures are given in degrees Centigrade.

## Example 1

3-{2-[(5-Methyl-1H-imidazol-4-yl)methylthio]ethylamino}-4-(2-propynyl)amino-1,2,5-thiadiazole 1,1-dioxide

A. 3-{2-[(5-Methyl-1H-imidazol-4-yl)methylthio]-ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide

To a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.0 g; 11.2 mmoles) [prepared according to the procedure described in J. Org. Chem., 40, 2743 (1975)] in 200 ml of methanol at ambient temperature was added a solution of 2-[(5-methyl-1H-imidazol-4-yl)-methylthio]ethylamine (from the dihydrochloride, 2.73 g; 11.2 mmoles) [prepared according to Belgian Patent 779,775] in 25 ml of methanol. After stirring for 30 minutes, a methanolic solution of the title compound was produced. The TLC (Silica/$CH_2Cl_2$:$CH_3OH$ (90:10)] gave Rf = 0.44.

B. 3-{2-[(5-Methyl-1H-imidazol-4-yl)methylthio]-ethylamino}-4-(2-propynyl)amino-1,2,5-thiadiazole 1,1-dioxide

To the methanolic solution of the product of Step A was added 7 ml of 2-propynylamine. After stirring at ambient temperature for 20 minutes, the reaction mixture was evaporated under reduced pressure, and the residual oil was placed on silica gel and chromatographed by gradient elution using methylene chloride-methanol. The appropriate fractions were combined to yield 2.74 g of the title compound as an oil.

An additional purification was achieved by combining the above material with that obtained in an identical second experiment and the mixture placed on silica gel and chromatographed by gradient elution using methylene chloride-methanol. The appropriate fractions were combined with methanol and evaporated under reduced pressure to yield the title compound (2.93 g) as a friable solid, mp 82-103°; the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the presence of 1/3 mole of methanol.

Anal. Calcd for $C_{12}H_{16}N_6O_2S_2 \cdot 1/3CH_3OH$: C, 42.19; H, 4.97; N, 23.95; S, 18.27.
Found: C, 42.05; H, 5.05; N, 24.01; S, 18.45.

## Example 2

### 3-{2-[(5-Methyl-1H-imidazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

To a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.5 g; 14.0 mmoles) in 250 ml of dry methanol that had been cooled to 2° in an ice-water bath was added dropwise over a period of 25 minutes a solution of 2-[(5-methyl-1H-imidazol-4-yl)methylthio]ethylamine (from the dihydrochloride, 3.42 g; 14.0 mmoles) in 25 ml of methanol. After stirring at 2° for 20 minutes, anhydrous methylamine was bubbled into the solution for 6 minutes and stirring was continued at ambient temperature for 30 minutes. The reaction mixture was evaporated under reduced pressure and the residue was placed on 50 g of silica gel and chromatographed by gradient elution using methylene chloride-methanol. The appropriate fractions

were combined to give 3.2 g of the title compound. Additional purification of the product using column chromatography gave an analytical sample of the title compound as an amorphous solid, mp 98-110°. The NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide gave the following resonances δ: 7.46 (s, 1H); 3.70 (s, 2H); 2.53 (t, 2H); 2.86 (s, 3H); 2.72 (t, 2H); 2.15 (s, 3H).

Anal. Calcd for $C_{10}H_{16}N_6O_2S_2$: C, 37.96; H, 5.09; N, 26.56; S, 20.27.

Found (corr. for 1.60% $H_2O$): C, 37.79; H, 5.16; N, 26.52; S, 20.24.

Example 3

3-{2-[(2-Guanidinothiazol-4-yl)methylthio]ethylamino}-4-{2-[(5-methyl-1H-imidazol-4-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

To a well stirred solution at -10° of 3-{2-[(5-methyl-1H-imidazol-4-yl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide [prepared from the dihydrochloride of 2-{(5-methyl-1H-imidazol-4-yl)methylthio}ethylamine (2.73 g; 11.2 mmole) by the procedure of Step A of Example 1] was rapidly added a solution of 2-[(2-guanidinothiazol-4-yl)methylthio]ethylamine (from the dihydrochloride, 3.41 g; 11.2 mmoles) [prepared according to the procedure described in South African Patent 78/2129] in 35 ml of methanol. After stirring at -10° for 30 minutes, the solution was allowed to warm to ambient temperature. The reaction mixture was evaporated under reduced pressure and the residue was placed on 45 g of silica gel and chromatographed using 1 liter of methylene chloride-methanol (4:1).

The appropriate fractions were combined and evaporated, and the residue (5.82 g) was placed on 80 g of aluminum oxide and chromatographed using a gradient elution of ethyl acetate-methanol. The appropriate fractions were combined, filtered through Celite and evaporated under high vacuum to yield the title compound (2.5 g) as an amorphous solid containing approximately 2/3 mole of ethyl acetate, as ascertained by the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide.

Anal. Calcd for $C_{16}H_{24}N_{10}O_2S_4 \cdot 2/3C_4H_8O_2$: C, 38.96; H, 5.14; N, 24.34; S, 22.29.

Found: C, 39.08; H, 4.96; N, 24.48; S, 22.26.

## Example 4

### 3-{2-[(5-Methyl-1H-imidazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide

#### A. 3,4-Dimethoxy-1,2,5-thiadiazole 1-oxide

A solution of 3,4-dimethoxy-1,2,5-thiadiazole (35.2 g; 24.1 mmoles) [prepared according to the procedure described in J. Org. Chem., 40, 2749 (1975)] in 100 ml of chloroform was added over a period of 3 minutes to a stirred solution of m-chloroperbenzoic acid (50.7 g; 25.0 mmoles; 85% assay) in 900 ml of chloroform at 20°, using a cooling bath to keep the exothermic reaction from rising above 32°. After stirring for 3 hours at ambient temperature, the excess peracid was reacted with an additional 2.0 g of 3,4-dimethoxy-1,2,5-thiadiazole and stirred for 1 hour.

The organic solution was extracted with two-300 ml portions of a 1% solution of $NaHCO_3$, washed with 250 ml of water, dried and evaporated under reduced pressure to give 47.0 g of product. Recrystallization from isopropyl alcohol gave the title compound (34.0 g). An additional recrystallization from isopropyl alcohol gave an analytical sample, mp 135-137°.

Anal. Calcd for $C_4H_6N_2O_3S$: C, 29.63; H, 3.72; N, 17.27; S, 19.77.

Found: C, 29.53; H, 3.75; N, 17.26; S, 19.83.

B. 3-{2-[(5-Methyl-1H-imidazol-4-yl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide

A solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide obtained from the above Step A is reacted with an equimolar amount of 2-[(5-methyl-1H-imidazol-4-yl)methylthio]ethylamine and the resulting 3-{2-[(5-methyl-1H-imidazol-4-yl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1-oxide is treated with an excess of methylamine, and the title compound is thereby produced.

## Example 5

3-{2-[(5-Hydroxymethyl-1H-imidazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

2-[(5-Hydroxymethyl-1H-imidazol-4-yl)methylthio]-ethylamine [prepared according to the procedure described in Belgian Patent 843,840] is reacted with 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide and the resultant 3-{2-[(5-hydroxymethyl-1H-imidazol-4-yl)methylthio]ethylamino}-4-methoxy-

1,2,5-thiadiazole 1,1-dioxide is treated with excess methylamine according to the general procedure described in Example 2, and the title compound is thereby produced.

Example 6

The general procedure of Example 5 is repeated except that the 2-[(5-hydroxymethyl-1H-imidazol-4-yl)-methylthio]ethylamine utilized therein is replaced by an equimolar amount of

2-[(5-bromo-1H-imidazol-4-yl)methylthio]ethylamine,
2-[imidazol-4-ylmethylthio]ethylamine,
2-[imidazol-2-ylmethylthio]ethylamine,
2-[(1-methyl-imidazol-2-yl)methylthio]ethylamine,
2-[(2-methyl-1H-imidazol-4-yl)methylthio]ethylamine,
2-[(1-methyl-imidazol-4-yl)methylthio]ethylamine,
2-[(1,5-dimethyl-imidazol-4-yl)methylthio]ethylamine,
2-[(5-chloro-1-methyl-imidazol-4-yl)methylthio]ethylamine,
2-[(5-trifluoromethyl-1H-imidazol-4-yl)methylthio]ethylamine,
2-[(5-ethyl-1H-imidazol-4-yl)methylthio]ethylamine and
2-[(2-amino-1H-imidazol-4-yl)methylthio]ethylamine,
respectively, [each prepared by the general procedures described in Belgian Patent 779,775] and there is thereby produced
3-{2-[(5-bromo-1H-imidazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[imidazol-4-ylmethylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[imidazol-2-ylmethylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,

3-{2-[(1-methyl-imidazol-2-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(2-methyl-1H-imidazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(1-methyl-imidazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(1,5-dimethyl-imidazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-chloro-1-methyl-imidazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-trifluoromethyl-1H-imidazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-ethyl-1H-imidazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide and
3-{2-[(2-amino-1H-imidazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide, respectively.

## Example 7

3-Hydroxy-4-{2-[(5-methyl-1H-imidazol-4-yl)methylthio]-ethylamino}-1,2,5-thiadiazole 1,1-dioxide

When a methanolic solution of 3-{2-[(5-methyl-1H-imidazol-4-yl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide [prepared by the procedure of Step A of Example 1] is treated with a solution of sodium hydroxide in methanol by the general procedure of Example 17, Step B, the title compound is produced, mp 263-265° (dec).

Anal. Calcd $C_9H_{13}N_5S_2O_3$: C, 35.64; H, 4.32; N, 23.09; S, 21.13.
Found: C, 35.56; H, 4.38; N, 23.01; S, 21.13.

Example 8

3-{4-[(2-Guanidino-1H-imidazol-4-yl]butylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A methanolic suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is successively reacted with an equimolar amount of 4-[2-guanidino-1H-imidazol-4-yl]-butylamine [prepared according to Belgian Patent 866,156] and excess methylamine according to the general procedure of Example 2, and the title compound is thereby produced.

Example 9

3-{2-[(5-Methyl-1H-imidazol-4-yl)methylthio]ethylamino}-4-(2-propynyl)amino-1,2,5-thiadiazole 1,1-dioxide

Reaction of a methanolic suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide with one equivalent of 2-propynylamine and treating the resultant 3-methoxy-4-propynylamino-1,2,5-thiadiazole 1,1-dioxide with one equivalent of 2-[(5-methyl-1H-imidazol-4-yl)methylthio]ethylamine yields the title compound; identical to the product of Example 1.

Example 10

3-{2-[(5-Methyl-1H-imidazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

When a solution of 3-methylamino-4-(2-mercapto-ethyl)-1,2,5-thiadiazole 1,1-dioxide (prepared in Example 25, Step A) is reacted with 4-chloromethyl-5-methylimidazole hydrochloride and a strong base, the title compound is thereby produced; identical to the product of Example 2.

## Example 11

### 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide and 3,4-bis-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

A. 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamine (2.41 g; 11.2 mmoles) [prepared according to the procedure described in Belgian Patent 857,388] in 20 ml of dry methanol was added all at once to a well stirred, cold (8°) suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.0 g; 11.2 mmoles) in 200 ml of methanol. After stirring at 8-10° for 15 minutes, a methanolic solution of the title compound is produced.

B. 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

Anhydrous methylamine was bubbled into the cooled (1°) methanolic solution of the product of Step A for 6 minutes. Stirring was continued for 10 minutes and the mixture was evaporated under reduced pressure. The residue

was placed on 45 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions, using methylene chloride-methanol (95:5) were combined in methanol, filtered through Celite, and then concentrated under reduced pressure to give product. Recrystallization from methanol yielded the title compound (1.76 g), mp 82-90°; the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the presence of 2/3 mole of methanol.

Anal. Calcd for $C_{13}H_{21}N_5O_3S_2 \cdot 2/3CH_3OH$: C, 43.10; H, 6.26; N, 18.38; S, 16.83.

Found (corr. for 1.72% $H_2O$): C, 43.30; H, 6.12; N, 18.57; S, 16.96.

C. 3,4-Bis-{2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

The slower eluting component using methylene chloride-methanol (9:1) from the chromatography in Step B was placed on 45 g of aluminum oxide and chromatographed using a gradient elution of ethyl acetate-methanol. The appropriate fraction was evaporated and the residue triturated under ether-acetonitrile to give a colorless solid which was collected by filtration to yield the title compound (428 mg) as a monohydrate, mp 92.5-96°.

Anal. Calcd for $C_{22}H_{34}N_6S_3O_4 \cdot H_2O$: C, 47.12; H, 6.47; N, 14.99; S, 17.15.

Found: C, 47.28; H, 6.48; N, 15.09; S, 17.39.

Calcd for $H_2O$ = 3.21%;

Found $H_2O$ = 3.32%

Example 12

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-ethylamino-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamine (2.41 g; 11.2 mmoles) in 20 ml of dry methanol was added all at once to a well stirred cold (1°) suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.0 g; 11.2 mmoles) in 200 ml of methanol. After stirring for 15 minutes at 1-5°, ethylamine (4.0 ml) was added and stirring was continued at approximately 5° for 20 minutes. The reaction mixture was evaporated under reduced pressure and the residue was placed on 46 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined, evaporated and the gelatinous residue triturated under ether and filtered to give the product as a colorless solid (2.81 g). Two recrystallizations from methanol and drying over $P_2O_5$ at ambient temperature for 17 hours yielded the title compound, mp 155-160° with variable sintering at 94-96°; the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the presence of approximately 0.8 moles of methanol.

Anal. Calcd for $C_{14}H_{23}N_5O_3S_2 \cdot 0.8CH_3OH$: C, 44.54; H, 6.62; N, 17.55; S, 16.07.

Found: C, 44.35; H, 6.58; N, 17.44; S, 16.18.

Example 13

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(2-propynyl)amino-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamine (2.41 g; 11.2 mmoles) in 20 ml of dry methanol was added dropwise over a period of 25 minutes to a well stirred cold (1°) suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.0 g; 11.2 mmoles) in 200 ml of methanol. After stirring at 1-2° for 15 minutes, a solution of 2-propynylamine (4.0 ml) in 10 ml of dry methanol was added all at once, and stirring was then continued at ambient temperature for 1 hour. The reaction mixture was evaporated under reduced pressure and the residue was placed on 50 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined, evaporated and crystallized from methanol to give 4.0 g of product. Recrystallization from methanol and then from isopropyl alcohol yielded the title compound (2.90 g), mp 92-100°; the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the product to be solvated with 1 mole of methanol.

Anal. Calcd for $C_{15}H_{21}N_5O_3S_2 \cdot CH_3OH$: C, 46.25; H, 6.06; N, 16.85; S, 15.43.

Found: C, 46.36; H, 6.22; N, 16.95; S, 15.73.

Example 14

3-Methylamino-4-{2-[(5-{[N-methyl-N-(2-propynyl)amino]-methyl}-2-furyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

A. 5-{[N-methyl-N-(2-propynyl)amino]methyl}-2-furanmethanol

To furfuryl alcohol (2.49 g; 25.4 mmoles) which was cooled in an ice-water bath to 5° was added N-methyl-propargylamine hydrochloride (4.0 g; 37.9 mmoles) and 40% formalin (3.13 ml; 41.7 mmoles), and the mixture stirred while allowed to reach ambient temperature. After 1 hour of stirring the solution was allowed to stand at ambient temperature for 4-1/2 days. The reaction mixture was poured into ice water, made strongly basic with 40% aqueous NaOH and extracted with five portions of methylene chloride. The combined organic phase was dried, filtered and evaporated under reduced pressure to give the product as an oil (quantitative yield). Vacuum distillation yielded the title compound, bp 102-106°/0.3 mm Hg.

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82
Found: C, 66.80; H, 7.44; N, 7.93

B. 2-[(5-{[N-Methyl-N-(2-propynyl)amino]-methyl}-2-furyl)methylthio]ethylamine

A solution of 5-{[N-methyl-N-(2-propynyl)amino]-methyl}-2-furanmethanol (40.0 g; 223 mmoles) [prepared in

Step A] in 100 ml of ice-cold concentrated HCl was added to a cold (5°) stirred solution of cysteamine hydrochloride (27.9 g; 24.6 mmoles) in 125 ml of concentrated hydrochloric acid. The solution was allowed to stand at 0° for 2-1/2 days, and then at ambient temperature for 7 hours to complete the reaction. The reaction mixture was cooled in an ice-water bath, diluted with 200 ml of water, made strongly alkaline with 40% aqueous NaOH, and then extracted with three portions of methylene chloride. The combined organic phase was dried, filtered, and evaporated under reduced pressure to give the product as a thick oil (46.4 g). A rapid vacuum distillation of the oil yielded the title compound, bp 136-140°/0.2 mm Hg.

Anal. Calcd for $C_{12}H_{18}N_2OS$: C, 60.47; H, 7.61; N, 11.76; S, 13.46.

Found: C, 59.82; H, 7.68; N, 11.61; S, 13.27.

C. 3-Methylamino-4-{2-[(5-{[N-methyl-N-(2-propynyl)amino]methyl-2-furyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

To a stirred cold (3°) suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.0 g; 11.2 mmoles) in 200 ml of dry methanol was added a solution of 2-[(5-{[N-methyl-N-(2-propynyl)amino]methyl}-2-furyl)methylthio]-ethylamine (2.68 g; 11.2 mmoles) [prepared in Step B]. After stirring at 3-7° for 15 minutes, methylamine was bubbled into the solution for 16 minutes. The reaction mixture was evaporated under reduced pressure and the oily residue was placed on 100 g of silica gel and chromatographed using a gradient of acetonitrile-methanol. The appropriate fractions were combined and rechromatographed on 100 g of silica gel using a gradient of methylene chloride-

methanol. The appropriate fractions was dissolved in methylene chloride and extracted with 1% aqueous NaOH. The aqueous phase was brought to pH 9 with 5% aqueous HCl and the separated oil was extracted with three portions of methylene chloride. The combined extracts were dried, filtered and evaporated under reduced pressure to give product as a foam. Recrystallization from isopropyl alcohol yielded the title compound, mp 50-51°, clear melt 54-56°; the NMR spectrum (100 MHz) in $D_6$ dimethyl sulfoxide showed the presence of approximately 1/4 mole of isopropyl alcohol.

Anal. Calcd for $C_{15}H_{21}N_5O_3S_2 \cdot 1/4C_3H_8O$: C, 47.47; H, 5.82; N, 17.57; S, 16.09.
Found: C, 47.51; H, 6.21; N, 16.40; S, 15.97.

## Example 15

### 3-{2-[(5-Dimethylaminomethyl-3-methyl-2-furyl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A. 5-Dimethylaminomethyl-3-methyl-2-furanmethanol

A mixture containing 3-methyl-2-furfuryl alcohol (11.2 g; 0.1 mole [prepared according to the procedure described in J. Am. Chem. Soc., 72, 2195 (1950)], dimethylamine hydrochloride (12.23 g; 0.15 mole) and 37% aqueous formaldehyde (12 ml, 0.15 mole) was stirred for 2.5 hours at approximately 5°, and then at ambient temperature overnight. The solution was heated for 10 minutes on a steam bath, diluted with 12 ml of water and basified with sodium carbonate. The mixture was extracted with ethyl acetate, and

the organic phase dried, filtered and evaporated under reduced pressure to yield the title compound, bp 88-96/0.05-0.08 mm Hg.

B. 2-[(5-Dimethylaminomethyl-3-methyl-2-furyl)-methylthio]ethylamine

To a solution of 2-aminoethanethiol hydrochloride (2.27 g; 20.0 mmoles) in 20 ml of concentrated HCl that was cooled in an ice-salt bath to -10° was added dropwise 5-dimethylaminomethyl-3-methyl-2-furanmethanol (3.38 g; 20.0 mmoles) [prepared in Step A], and the mixture stirred for 15 minutes then allowed to stand in the cold (0°) overnight. After 17 hours the cold solution was made strongly basic with aqueous KOH solution and then extracted with five portions of methylene chloride. The combined organic phase was dried, filtered and evaporated under reduced pressure to yield the title compound (4.16 g), bp 110-120°/ 0.1 mm Hg.

C. 3-{2-[(5-Dimethylaminomethyl-3-methyl-2-furyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

When a methanol suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is reacted with an equimolar amount of 2-[(5-dimethylaminomethyl-3-methyl-2-furyl)methylthio]ethylamine [prepared in Step B] and the resultant 3-{2-[(5-dimethylaminomethyl-3-methyl-2-furyl)methylthio]-ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide is treated with an excess of methylamine, the title compound is thereby produced.

## Example 16

### 3-{2-[(5-Dimethylaminomethyl-4-methyl-2-furyl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

#### A. 2-Dimethylaminomethyl-3-methylfuran

A stirred solution of 3-methyl-2-furfuryl alcohol (25.2 g; 22.5 mmoles) and triethylamine (27.3 g; 27.0 mmoles) in 200 ml of methylene chloride was cooled to -15° in an ice-salt bath and a solution of thionyl chloride (18.0 ml, 24.8 mmoles) in 30 ml of methylene chloride was added dropwise, keeping the temperature between -10 to -15°. After 15 minutes, the mixture was poured into ice-water and the organic layer was separated. The methylene chloride phase containing 3-methyl-2-chloromethylfuran was added to a stirred solution, at 0°, of dimethylamine (137.0 g; 3.04 moles) in 400 ml of absolute ethanol and the resulting solution was stirred at ambient temperature for 17 hours. The reaction mixture was evaporated under reduced pressure and the residue was mixed with 400 ml of water, made strongly basic with 40% aqueous NaOH and extracted with five portions of methylene chloride. The combined extracts were dried, filtered and evaporated under reduced pressure to yield 26.0 g of the title compound, bp 64-70°/20 mm Hg. A TLC [Silica/$CHCl_3$:$CH_3OH$ (85:15)] gave Rf = 0.50.

#### B. 2-Chloromethyl-5-dimethylaminomethyl-3-methylfuran

To a solution of 2-dimethylaminomethyl-3-methyl-furan (6.5 g; 37.0 mmoles) [prepared in Step A] in 250 ml

of chloroform was added paraformaldehyde (1.67 g; 55.7 mmoles) and zinc chloride (312 mg), and a slow stream of HCl gas was bubbled through while stirring at ambient temperature for 15 minutes. Stirring was continued for 2 hours, then HCl gas was bubbled through for 15 minutes and the mixture stirred for 1 hour. At this time additional paraformaldehyde (1.67 g; 55.7 mmoles) was added to the reaction mixture and a slow stream of HCl gas was passed through for 15 minutes. After stirring at ambient temperature for 18 hours, the reaction mixture was filtered through Celite and the filtrate evaporated under reduced pressure to yield the title compound (4.97 g) which crystallized upon standing and was used without further purification in Step C.

The NMR spectrum (60 MHz) in $CDCl_3$ gave the following resonances δ: 6.33 (s, 1H); 4.55 (s, 2H); 4.30 (d, 2H); 2.83 (d, 6H); 2.13 (s, 3H)

C. 2-[(5-Dimethylaminomethyl-4-methyl-2-furyl)-methylthio]ethylamine

To a solution of 2-chloromethyl-5-dimethylaminomethyl-3-methylfuran (773 mg, 3.45 mmoles) [prepared in Step B] in 20 ml of concentrated hydrochloric acid that was cooled in an ice-water bath was added 2-aminoethanethiol hydrochloride (392 mg, 3.45 mmoles), and the mixture was stirred for 30 minutes. The solution was allowed to stand at 0° for 3 days, then made strongly basic with 50% aqueous KOH, diluted with water and extracted with five portions of methylene chloride. The combined extract was dried, filtered and evaporated under reduced pressure to

yield the title compound as an oil.

The product was dissolved in absolute ethanol, treated with anhydrous hydrogen chloride and evaporated under reduced pressure. The residue was dissolved in hot isopropyl alcohol, treated with charcoal, filtered and concentrated to crystallize the hydrochloride salt. Recrystallization from isopropyl alcohol yielded the title compound as the dihydrochloride salt, mp 185-190° (dec).

D. 3-{2-[(5-Dimethylaminomethyl-4-methyl-2-furyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

When a methanol suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is reacted with an equimolar amount of 2-[(5-dimethylaminomethyl-4-methyl-2-furyl)methylthio]ethylamine [prepared in Step C] and the resultant 3-{2-[(5-dimethylaminomethyl-4-methyl-2-furyl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide is treated with an excess of methylamine, the title compound is produced.

## Example 17

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-hydroxy-1,2,5-thiadiazole 1,1-dioxide

A. 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(5-dimethylaminomethyl-2-furyl-

methylthio]ethylamine (2.14 g; 10.0 mmoles) in 25 ml of dry methanol was added dropwise over 35 minutes to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (1.78 g; 10.0 mmoles) in 180 ml of dry methanol that had been cooled to 1° in an ice-water bath. After 15 minutes at 0°, a methanol solution of the title compound is produced. A TLC [silica/$CH_2Cl_2$:$CH_3OH$ (9:1)] gave Rf = 0.48.

A 2.0 ml aliquot of the solution was made acidic with 6.0N HCl and evaporated under reduced pressure without heating to yield the title compound as the hydrochloride salt. The NMR spectrum (100 MHz) in $D_2O$ gave the following resonances δ: 6.45 (d, 1H); 6.19 (d, 1H); 4.14 (s, 2H); 4.0 (s, 3H); 3.64 (s, 2H); 3.37 (t, 2H); 2.65 (s, 6H); 2.61 (t, 2H).

B. 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-hydroxy-1,2,5-thiadiazole 1,1-dioxide

To the methanolic solution of the product of Step A, cooled to 0° in an ice-water bath, was added a solution of sodium hydroxide pellets (2.10 g; 52.5 mmoles) in 25 ml of dry methanol. After stirring at 0° for 2 hours and at ambient temperature for 68 hours, the reaction mixture was neutralized with 8.75 ml (52.5 mmoles) of aqueous 6.0N HCl and after 10 minutes of stirring was evaporated under reduced pressure. The residue was crystallized under 95% EtOH to give crude product which was dissolved in methanol, filtered to remove sodium chloride, placed on 60 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were

combined and evaporated under reduced pressure to give 3.19 g of product. Recrystallization from aqueous methanol yielded the title compound, mp 109-122°.

Anal. Calcd for $C_{12}H_{18}N_4O_4S_2$: C, 41.61; H, 5.24; N, 16.17; S, 18.51.

Found (corr. for 1.15% $H_2O$): C, 41.59; H, 5.32; N, 16.33; S, 18.81.

## Example 18

### 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide

A. 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1-oxide

A solution of 2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamine (3.30 g; 15.4 mmoles) in 25 ml of methanol was added dropwise over a period of 14 minutes to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (2.50 g; 15.4 mmoles) [prepared according to the procedure in Example 4, Step A] that was cooled to 12-15° in an ice-water bath. The solution was stirred at ambient temperature for 1.5 hours to yield a methanolic solution of the title compound.

B. 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide

To the methanolic solution of the product of Step A that was cooled to 5° in an ice-water bath was added

anhydrous methylamine for 8 minutes. The reaction mixture was stirred at ambient temperature for 17 hours, then evaporated under reduced pressure to give the product as a yellow oil that was placed on 55 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fraction was evaporated, dissolved in methanol and diluted with diethyl ether to yield the title compound (2.32 g) as a solid that was dried *in vacuo* at ambient temperature over $P_2O_5$ for 3 hours, mp 86-92°.

Anal. Calcd for $C_{13}H_{21}N_5O_2S_2$: C, 45.46; H, 6.16; N, 20.39; S, 18.67.
Found: C, 45.24; H, 6.24; N, 20.41; S, 18.90.

Example 19

3-Allylamino-4-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

To a partial suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.08 g; 11.7 mmoles) in 200 ml of methanol that had been cooled to 0° in an ice-water bath was added dropwise over a period of 45 minutes a solution of 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine in 30 ml of methanol. When the addition was completed, 10.5 ml of allylamine was added and the solution was allowed to stir at ambient temperature for 18 hours. The reaction mixture was evaporated under reduced pressure and the residue was placed on 120 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol.

The appropriate fractions were combined, evaporated under reduced pressure and the residue crystallized with isopropyl alcohol to give the title compound, mp 83-86°; the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the presence of approximately 0.9 moles of isopropyl alcohol. Anal. Calcd for $C_{15}H_{23}N_5O_3S_2 \cdot 0.9C_3H_8O$: C, 48.36; H, 6.92; N, 15.93; S, 14.59. Found: C, 48.46; H, 6.96; N, 16.13; S, 14.58.

## Example 20

3-Methylamino-4-{2-[(5-methylaminomethyl-2-furyl)methylthio]-ethylamino}-1,2,5-thiadiazole 1,1-dioxide and 3,4-bis-{2-[(5-methylaminomethyl-2-furyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

### A. 3-Methylamino-4-{2-[(5-methylaminomethyl-2-furyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

To a partial suspension of 3,4-dimethoxy-1,2,5-thiadiazole (1.89 g; 10.5 mmoles) in 210 ml of methanol that was cooled to 8° was added all at once a solution of 2-[(5-methylaminomethyl-2-furyl)methylthio]ethylamine (0.7 g; 3.51 mmoles) [prepared according to the procedure described in Belgian Patent 857,388] in 21 ml of methanol. The mixture was stirred for 15 minutes and cooled to 1° in an ice-water bath, and anhydrous methylamine then was bubbled into the solution for 6 minutes. After stirring for 15 minutes the reaction mixture was evaporated under reduced pressure and the residue placed on 110 g of silica gel using a gradient elution from acetonitrile to acetonitrile-methanol-glacial acetic acid (50:50:0.5). The

appropriate fractions containing the first eluting component with Rf = 0.50 [TLC-silica/$CH_3CN$:$CH_3OH$:$CH_3COOH$ (50:50:1)] were combined and evaporated under reduced pressure to yield the title compound as a foam, mp 50-56°.

The NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide gave the following resonances δ: 6.20 (m, 2H); 3.80 (s, 2H); 3,62 (s, 2H); 3.50 (t, 2H); 2.90 (s, 3H); 2.70 (t, 2H); 2.28 (s, 3H); it also showed the presence of approximately 0.2 mole of methanol.

Anal. Calcd for $C_{12}H_{19}N_5O_3S_2 \cdot 0.2\ CH_3OH$: C, 41.65; H, 5.65; N, 19.96; S, 18.28.

Found (corr. for 1.42% $H_2O$): C, 41.98; H, 5.69; N, 19.54; S, 18.54.

B. 3,4-Bis-{2-[(5-methylaminomethyl-2-furyl)-methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

The fractions containing the slower eluting component from the chromatography in Step A with Rf = 0.07 [TLC-silica/$CH_3CN$:$CH_3OH$:$CH_3COOH$ (50:50:1)] were combined, evaporated and the residue partitioned between 2.5N NaOH and ethyl acetate. The aqueous phase was extracted with several portions of ethyl acetate and the combined organic layer was dried and evaporated under reduced pressure to give the title compound as an oil.

The NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide gave the following resonances δ: 6.22 (m, 4H); 3.82 (s, 4H); 3.65 (s, 4H); 3.50 (t, 4H); 2.72 (t, 4H); 2.30 (s, 6H).

## Example 21

**3-{4-(5-Dimethylaminomethyl-2-furyl)butylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide**

A solution of 4-(5-dimethylaminomethyl-2-furyl)-butylamine (1.5 g; 7.64 mmoles) [prepared according to the procedure described in U.S. Patent 4,128,658] in 40 ml of dry methanol was added dropwise over a period of 45 minutes to a stirred solution of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (1.36 g; 7.64 mmoles) in 200 ml of dry methanol that had been cooled to 3° in an ice-water bath. After 15 minutes at 3°, anhydrous methylamine was bubbled into the cooled solution for 10 minutes. The reaction mixture was evaporated under reduced pressure and the residue placed on 60 g of silica gel and chromatographed using a gradient elution of acetonitrile-methanol. The appropriate fractions were combined to give 2.16 g of product. Recrystallization from acetonitrile yielded the title compound, mp 152-153°.

Anal. Calcd for $C_{14}H_{23}N_5O_3S$: C, 49.25; H, 6.79; N, 20.51; S, 9.39.

Found: C, 49.41; H, 6.87; N, 20.61; S, 9.28

Example 22

3-{2-[(5-Dimethylaminomethyl-2-furyl)methoxy]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

When a methanolic suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is reacted with one equivalent of 2-[(5-dimethylaminomethyl-2-furyl)methoxy]-ethylamine [prepared according to U.S. Patent 4,128,658] and then with excess methylamine, the title compound is thereby produced.

Example 23

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-ethylamino-1,2,5-thiadiazole 1,1-dioxide

Reaction of a methanolic suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide with one equivalent of ethylamine and treatment of the resultant 3-methoxy-4-ethylamino-1,2,5-thiadiazole 1,1-dioxide with one equivalent of 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine yields the title compound, which is identical to the product prepared in Example 12.

Example 24

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide

Reaction of a methanolic solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide [prepared in Example 4, Step A]

with one equivalent of methylamine and treatment of the resultant 3-methoxy-4-methylamino-1,2,5-thiadiazole 1-oxide with one equivalent of 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine yields the title compound, which is identical to the product prepared in Example 18.

## Example 25

### 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A, 3-Methylamino-4-(2-mercaptoethyl)-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-aminoethanethiol (from the hydrochloride 1.91 g; 16.8 mmoles) in 20 ml of methanol was added dropwise over a period of 15 minutes to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (3.0 g; 16.8 mmoles) in 250 ml of methanol that had been cooled to 1° in an ice-water bath. After 10 minutes at 2-4°, methylamine was bubbled into the cooled solution for 6 minutes and stirring was continued for an additional 30 minutes at ambient temperature. The reaction mixture was evaporated under reduced pressure and the residue placed on 45 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined and evaporated, and the product (2.43 g) was crystallized from absolute ethanol. Recrystallization from absolute ethanol yielded the title compound, mp 259-260° (dec).

Anal. Calcd for $C_5H_{10}N_4O_2S_2$: C, 27.03; H, 4.54; N, 25.20.
Found: C, 27.13; H, 4.55; N, 24.86.

B. 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A mixture containing 3-methylamino-4-(2-mercaptoethyl-1,2,5-thiadiazole 1,1-dioxide (1.0 g; 4.5 mmoles) [prepared in Step A] and 5-dimethylaminomethyl-2-furanmethanol (0.82 g; 4.5 mmoles) [prepared according to the procedure in J. Chem. Soc., 4728 (1958)] in 20 ml of concentrated hydrochloric acid was stirred in an ice-water bath for 2 hours and then allowed to stand at 0° for 64 hours. The reaction mixture was stirred at ambient temperature for 23 hours, evaporated without heating under reduced pressure and the residue partitioned between water and methylene chloride. The aqueous phase was made basic with sodium bicarbonate and extracted with methylene chloride. The combined organic phase was washed with saturated brine solution, dried and evaporated under reduced pressure. The residue was placed on 25 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fraction was evaporated and the product crystallized from methanol. Recrystallization from methanol yielded the title compound, mp 92-96°.

## Example 26

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide

A. 3-Methylamino-4-(2-mercaptoethyl)-1,2,5-thiadiazole 1-oxide

A solution of 2-aminoethanethiol (from the hydrochloride, 2.04 g; 18.0 mmoles) in 25 ml of methanol was added dropwise over a period of 30 minutes to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1-dioxide (2.92 g; 18.0 mmoles) [prepared in Example 4, Step A] in 150 ml of methanol that had been cooled to 3° in an ice-water bath. After 10 minutes, anhydrous methylamine was bubbled into the solution for 6 minutes and stirring was continued at ambient temperature for an additional 20 minutes. The reaction mixture was evaporated under reduced pressure and the residue placed on 45 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined and evaporated to give 2.74 g of product. Recrystallization from methanol and then 95% ethanol yielded the title compound, mp 191-193°.

B. 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide

When 3-methylamino-4-(2-mercaptoethyl)-1,2,5-thiadiazole 1-oxide [prepared in Step A] is treated with about one equivalent of 5-dimethylaminomethyl-2-furanmethanol in concentrated hydrochloric acid according to the procedure described in Example 25, Step B, the title compound is thereby produced; identical to the product of Example 18.

Example 27

3-{3-[(5-Dimethylaminomethyl-2-furyl)methylthio]propyl-amino}-4-ethylamino-1,2,5-thiadiazole 1,1-dioxide

When 1-phthalimido-3-[(5-dimethylaminomethyl-2-furyl)methythio]propane [prepared according to the procedure described in Belgian Patent 857,388] is treated with hydrazine, and the resulting substituted propylamine is reacted according to the general procedure of Example 12, the title product is thereby produced.

Example 28

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethyl-amino}-4-dimethylamino-1,2,5-thiadiazole 1,1-dioxide

To a cooled (6°) partial suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.08 g; 11.7 mmoles) in 200 ml of methanol was added dropwise over a period of 45 minutes a solution of 2-[(5-dimethylamino-methyl-2-furyl)methylthio]ethylamine (2.5 g; 11.7 mmoles) in 50 ml of methanol. When the addition was completed, anhydrous dimethylamine was bubbled into the solution for 10 minutes while maintaining the temperature at 6°. After stirring at ambient temperature for 18 hours, the reaction mixture was evaporated under reduced pressure and the residue placed on 200 g of silica and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined and evaporated and the residue was rechromatographed on 75 g of aluminum oxide using a gradient elution of methylene chloride-

methanol. The appropriate fractions were combined and evaporated under reduced pressure to give the title compound, mp 139-142°.

Anal. Calcd for $C_{19}H_{24}N_5O_3S_2$: C, 44.90; H, 6.46; N, 18.70; S, 17.12.

Found (corr. for 0.51% $H_2O$): C, 44.77; H, 6.25; N, 18.89; S, 17.42.

Example 29

The general procedure of Example 28 is repeated, except that the dimethylamine utilized therein is replaced by

thiomorpholine,
piperazine,
N-acetylpiperazine,
N-methylpiperazine,
hexamethyleneimine and
homopiperazine, respectively,

and there is thereby produced

3-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(4-thiomorpholinyl)-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(1-piperazinyl)-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(4-acetyl-1-piperazinyl)-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(4-methyl-1-piperazinyl)-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(1-hexamethyleneimino)-1,2,5-thiadiazole 1,1-dioxide and
3-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(1-homopiperazinyl)-1,2,5-thiadiazole 1,1-dioxide,

respectively.

Example 30

The general procedure of Example 13 is repeated, except that the 2-propynylamine utilized therein is replaced by an equimolar amount of
cyclobutylamine,
aminomethylcyclobutane,
ethanolamine,
2-methylthioethylamine,
2,2,2-trifluoroethylamine,
2-fluoroethylamine,
ethylenediamine,
2-methylaminoethylamine,
2-dimethylaminoethylamine,
1,1-dimethylhydrazine,
cyanamide,
3-aminopropionitrile,
guanidine and
methylguanidine, respectively,
and there is thereby produced
3-(cyclobutylamino)-4-{2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide,
3-[(cyclobutyl)methylamino]-4-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(2-hydroxyethylamino)-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(2-methylthioethylamino)-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(2,2,2-trifluoroethylamino)-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(2-fluoroethylamino)-1,2,5-thiadiazole 1,1-dioxide,

3-(2-aminoethylamino)-4-{2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(2-methylaminoethylamino)-1,2,5-thiadiazole 1,1-dioxide.
3-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(2-dimethylaminoethylamino)-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(2,2-dimethylhydrazino)-1,2,5-thiadiazole 1,1-dioxide,
3-cyanoamino-4-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide,
3-(3-cyanopropylamino)-4-{2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-guanidino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(N'-methyl)guanidino-1,2,5-thiadiazole 1,1-dioxide.

Example 31

3-{2-[(2-Guanidinothiazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(2-guanidinothiazol-4-yl)methylthio]ethylamine (from the dihydrochloride, 4.27 g; 14.0 mmoles) in 30 ml of methanol was added to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.50 g; 14.0 mmoles) in 250 ml of methanol at 10°. After 15 minutes at 10°, the solution was cooled to 1° in a cooling bath and anhydrous methylamine was bubbled into the solution for 10 minutes. The reaction mixture was evaporated under reduced pressure and the residue placed on 60 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fraction

containing 4.53 g of product was placed on 80 g of aluminum oxide and rechromatographed using a gradient elution of ethyl acetate-methanol. The appropriate fractions were combined and evaporated to give a foam which crystallized from methanol to yield (2.38 g) of the title compound, mp 196-198° (dec).

Anal. Calcd for $C_{10}H_{16}N_8O_2S_3$: C, 31.90; H, 4.28; N, 29.77; S, 25.55.

Found: C, 31.85; H, 4.24; N, 29.79; S, 25.45.

## Example 32

### 3-{2-[(2-Guanidinothiazol-4-yl)methylthio]ethylamino}-4-(2-propynyl)amino-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(2-guanidinothiazol-4-yl)methylthio]ethylamine (from the dihydrochloride, 3.42 g; 11.2 mmoles) in 25 ml of methanol was added to a well stirred cold (8°) suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.0 g; 11.2 mmoles) in 200 ml of methanol. After 15 minutes at 8-10°, the solution was cooled to 1° in an ice-bath and a solution of 6.0 ml 2-propynylamine in 15 ml of methanol was added. The ice-bath was removed and stirring was continued for 15 minutes. The reaction mixture was evaporated under reduced pressure and the residue placed on 50 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. Two of the fractions yielded crystalline product (1.74 g) from methanol. The product was dissolved in hot methanol, filtered through Celite, cooled and filtered to yield the title compound, mp 176-178°.

Anal. Calcd for $C_{12}H_{16}N_8O_2S_3$: C, 35.99; H, 4.03; N, 27.98; S, 24.02.
Found: C, 35.82; H, 4.12; N, 28.41; S, 24.28.

## Example 33

### 3-{2-[(2-Dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

#### A. N-Carbophenoxy-N-methylaminoacetonitrile

To a suspension of methylaminoacetonitrile hydrochloride (100 g; 0.94 mole) in 1 liter of methylene chloride (cooled in an ice-water bath) was added triethylamine (260 ml, 1.88 moles) and a solution of phenyl chloroformate (155.0 g; 0.99 mole) in 500 ml of methylene chloride. The reaction mixture was heated at reflux temperature for 18 hours, then evaporated under reduced pressure to give a semi-solid which was triturated with 1 liter of diethyl ether and filtered. The filtrate was evaporated under reduced pressure and the residual oil was vacuum distilled to yield the title compound (123 g), bp 111-113°/0.25 mm Hg; the NMR spectrum (60 MHz) in $CDCl_3$ gave the following resonances δ: 7.23 (m, 5H); 4.30 (s, 2H); 3.13 (s, 3H).

#### B. (N-Carbophenoxy-N-methylamino)thioacetamide

A solution of N-carbophenoxy-N-methylaminoacetonitrile (131.0 g; 0.69 mole) [prepared in Step A] and thioacetamide (57.1 g; 0.71 mole) in 917 ml of dry DMF was treated with HCl gas until an exothermic reaction took place, and then heated on a steam bath for 20 minutes.

The reaction mixture was partially evaporated under reduced pressure to remove some of the solvent, then made basic with saturated aqueous $NaHCO_3$ solution and partitioned between ether and water. The aqueous phase was extracted with ether and the combined ether phase was washed with water, saturated aqueous NaCl solution and dried. Filtration and evaporation of the solvent gave an oil which was triturated with methylcyclohexane to give the product as a solid. Recrystallization from isopropyl alcohol yielded the title compound, mp 101-103°.

Anal. Calcd $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.40; N, 12.49; S, 14.30.

Found: C, 53.65; H, 5.51; N, 12.69; S, 14.41.

C. 4-Chloromethyl-2-(N-carbophenoxy-N-methylamino)methylthiazole

To a cooled solution of (N-carbophenoxy-N-methylamino)thioacetamide (1.0 g; 4.46 mmoles) and dry pyridine (0.36 ml, 4.46 mmoles) in 6 ml of absolute ethanol was added a solution of 1,3-dichloropropanone (0.57 g; 4.49 mmoles) in 3 ml of absolute ethanol. The mixture was heated at reflux temperature for 1.5 hours, then evaporated under reduced pressure and the oil residue partitioned between ether and water. The aqueous layer was extracted with ether and the combined ether phase was washed with water, saturated aqueous sodium chloride solution and dried. Filtration and evaporation yielded 1.02 g of the title compound as a viscous oil; TLC [silica/$CH_2Cl_2$:$CH_3CN$ (85:15)] gave Rf = 0.82. The NMR spectrum (60 MHz) in $CDCl_3$ gave the following resonances δ: 7.16 (m, 6H); 4.77 (broad s, 2H); 4.60 (s, 2H); 3.07 (broad s, 3H).

D. 2-{[2-(N-Carbophenoxy-N-methylamino)methyl-4-thiazolyl]methylthio}ethylamine

To a solution of sodium methoxide (26.1 g; 0.48 mole) in 290 ml of absolute ethanol at 0° under a nitrogen atmosphere was added cysteamine hydrochloride (27.6 g; 0.24 mole) and an additional 218 ml of absolute ethanol. After stirring at 0° for 1 hour a solution of 4-chloromethyl-2-(N-carbophenoxy-N-methylamino)methylthiazole (72.5 g; 0.24 mole) in 218 ml of absolute ethanol was added over a 15 minute period. The reaction mixture was stirred at ambient temperature for 18 hours, filtered and evaporated under reduced pressure to give an oil which was partitioned between methylene chloride and water. The aqueous phase was extracted with methylene chloride and the combined organic phase was washed with water, dried, filtered and evaporated under reduced pressure to give the product (68.5 g) as an oil which was treated with fumaric acid (23.6 g) in n-propanol to give the salt (47.0 g). Recrystallization from absolute ethanol yielded the title compound as the fumarate salt, mp 145-146°.

Anal. Calcd for $C_{15}H_{19}N_3O_2S_2 \cdot C_4H_4O_4$: C, 50.31; H, 5.11; N, 9.27; S, 14.14.

Found: C, 50.02; H, 5.16; N, 9.47; S, 14.22.

E. 2-[(2-Dimethylaminomethyl-4-thiazolyl)-methylthio]ethylamine

To a solution of 2-{[2-(N-Carbophenoxy-N-methylamino)methyl-4-thiazolyl]methylthio}ethylamine (0.50 g;

1.48 mmoles) [prepared in Step D] in 10 ml of dry tetrahydrofuran under a nitrogen atmosphere was added lithium aluminum hydride (0.17 g.; 4.48 mmoles) and the mixture was heated at reflux temperature for 0.5 hour. An additional 10 ml of tetrahydrofuran was added and heating was continued for 3 hours. The reaction mixture was treated with 0.17 ml of $H_2O$, 0.17 ml of 15% aqueous NaOH and 0.51 ml of $H_2O$, and filtered through Celite and dried. The filtrate was filtered and evaporated under reduced pressure to give an oil which was dissolved in absolute ethanol, diluted with diethyl ether and acidified with dry HCl. The hydroscopic hydrochloride salt of the title compound was collected and partitioned between aqueous 2.5N NaOH and methylene chloride. The organic phase was washed with water, dried and filtered. The filtrate was evaporated under reduced pressure to give the free base of the title compound as an oil (0.22 g; 0.95 mmole) which was combined with anhydrous oxalic acid (0.24 g; 1.90 mmole) in 30 ml of hot acetonitrile. The mixture was evaporated from hot absolute ethanol to yield the title compound the bis-oxalate, mp 168-171°.

Anal. Calcd for $C_9H_{17}N_3O_4S_2 \cdot 2C_2H_2O_4$: C, 37.95; H, 5.15; N, 10.21; S, 15.59.

Found: C, 37.95; H, 5.04; N, 9.81; S, 15.27.

F. 3-{2-[(2-Dimethylaminomethyl-4-thiazolyl)-methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

To a cooled (6°) suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (0.74 g; 4.17 mmoles) in 80 ml of methanol was added dropwise over a period of 45 minutes a solution of 2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamine (0.96 g; 4.17 mmoles) [prepared in Step E] to give 3-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide, Rf = 0.64 [Silica/$CH_2Cl_2$:$CH_3OH$ (9:1)]. The temperature was maintained at 6° and anhydrous methylamine was bubbled into the solution for 8 minutes. The reaction mixture was evaporated under reduced pressure and the residue placed on 80 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined and the residue was rechromatographed on 25 g of aluminum oxide using a gradient elution of methylene chloride-methanol to give 0.52 g of product. Recrystallization from isopropyl alcohol/ether yielded the title compound, mp 144-148° (foaming).

Anal. Calcd for $C_{12}H_{20}N_6O_2S_3$: C, 38.28; H, 5.35; N, 22.32; S, 25.55.

Found: C, 37.89; H, 5.43; N, 22.19; S, 25.40.

## Example 34

### 3-{2-[(2-Dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide

#### A. N-Carbethoxy-N-methylaminoacetonitrile

Triethylamine (5.2 ml; 37.6 mmoles) was added to a

suspension of methylaminoacetonitrile hydrochloride (2.0 g; 18.8 mmoles) in 20 ml of methylene chloride. The resulting suspension was cooled in an ice-bath and a solution of ethyl chloroformate (2.14 g; 19.8 mmoles) in 10 ml of methylene chloride was added over a 0.5 hour period, and the mixture was then heated at reflux temperature for 18 hours. The reaction mixture was evaporated under reduced pressure to give a semi-solid residue which was triturated with diethyl ether and filtered, and the filtrate was evaporated under reduced pressure to yield the title compound as an oil (2.2 g), bp 96-98°/5.2 mm Hg.

B. (N-Carbethoxy-N-methylamino)thioacetamide

A solution of N-carbethoxy-N-methylaminoacetonitrile (9.8 g; 6.9 mmoles) [prepared in Step A], and thioacetamide (10.35 g; 13.8 mmoles) in 175 ml of dry DMF was treated with hydrogen chloride gas until a vigorous exothermic reaction took place, and then was heated on a steam bath for 15 minutes. The reaction mixture was made basic with saturated $NaHCO_3$ solution, and then extracted with ether, washed with water and dried. The etheral phase was evaporated under reduced pressure to give a solid residue which was dissolved in methylene chloride and washed with water. The organic phase was dried, filtered and evaporated under reduced pressure to give product (2.5 g). Recrystallization from ethyl acetate-hexane yielded the title compound, mp 91-93°.

Anal. Calcd for $C_6H_{12}N_2O_2S$: C, 40.89; H, 6.87; N, 15.96; S, 18.92.
Found: C, 40.73; H, 6.85; N, 16.13; S, 18.86.

C. 2-(N-Carbethoxy-N-methylamino)methyl-4-carbethoxythiazole

To a solution of (N-carbethoxy-N-methylamino)-thioacetamide (30.7 g; 0.17 mole) [prepared in Step B] in 180 ml of absolute ethanol was added a solution of ethyl bromopyruvate (25.0 ml; 0.20 mole) in 130 ml of absolute ethanol. The reaction mixture was heated at reflux temperature for 17 hours and then evaporated under reduced pressure, and the residue was partitioned between ether and water. The organic layer was washed with water and saturated sodium chloride solution, dried, filtered and evaporated under reduced pressure to give an oil which was placed on silica gel and chromatographed using diethyl ether as the eluting solvent. The appropriate fractions yielded the title compound as an oil; TLC [Silica/$CH_2Cl_2$:$CH_3$-CN (85:15)] gave Rf = 0.50. The NMR spectrum (60 MHz) in $d_6$ dimethyl sulfoxide gave the following resonances δ: 8.49 (s, 1H); 4.79 (s, 2H); 4.23 (m, 4H); 3.00 (s, 3H); 1.30 (q, 6H).

D. 2-Dimethylaminomethyl-4-hydroxymethylthiazole

To a cooled suspension of lithium aluminum hydride (8.4 g; 0.22 mole) in 80 ml of dry tetrahydrofuran was added a solution of 2-(N-carbethoxy-N-methylamino)methyl-4-carbethoxythiazole (20.0 g; 0.07 mole) [prepared in Step C]

in 160 ml of dry tetrahydrofuran over a 1 hour period. The reaction mixture was heated at reflux temperature for 8 hours, then cooled and decomposed with $Na_2SO_4$ and 40% aqueous potassium hydroxide. The mixture was filtered, dried and evaporated under reduced pressure to give 4.2 g of the title compound as an oil; TLC (aluminum oxide/$CH_3CN$) gave RF = 0.45. The NMR spectrum (60 MHz) in $CDCl_3$ gave the following resonances δ: 7.17 (s, 1H); 4.73 (d, 2H); 3.43 (s, 2H); 3.35 (s, 6H).

E. 2-[(2-Dimethylaminomethyl-4-thiazolyl)methylthio]ethylamine

When 2-dimethylaminomethyl-4-hydroxymethylthiazole [prepared in Step D] is reacted with thionyl chloride and the resultant 2-dimethylaminomethyl-4-chloromethylthiazole is reacted with an equimolar amount of cysteamine hydrochloride and two equivalents of base according to the general procedure of Example 33, Step D, the title compound is thereby produced.

F. 3-{2-[(2-Dimethylaminomethyl-4-thiazolyl)-methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide

When a methanol suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide [prepared in Example 4, Step A] is reacted with an equimolar amount of 2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamine [prepared in Example 33, Step E] and the resulting 3-{2-[(2-dimethylaminomethyl-4- thiazolyl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1-oxide is treated with methylamine, the

title compound is thereby produced.

Example 35

3-Amino-4-{2-[(2-guanidinothiazol-4-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(2-guanidinothiazol-4-yl)methylthio]ethylamine (2.75 g; 11.9 mmoles) [obtained by neutralization of 2-[(2-guanidinothiazol-4-yl)methylthio]ethylamine dihydrochloride (4.0 g; 13.0 mmoles) with 2.5N aqueous sodium hydroxide and extraction with ethyl acetate] in 30 ml of methanol was added over a 1 hour period to a well stirred, cold (0°) suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.12 g; 11.9 mmoles) in 220 ml of methanol. While maintaining the temperature at 0°, anhydrous ammonia was bubbled into the solution for 6 minutes and stirring was continued at ambient temperature for 0.5 hour. The reaction mixture was evaporated under reduced pressure and the residue placed on 120 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined and evaporated, and the residue was rechromatographed on 40 g of silica gel using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined, concentrated under vacuum, filtered and dried under high vacuum to yield the title compound, mp 134-149° (foaming); the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide/$D_2O$/DCl gave the following resonances δ: 7.16 (s, 1H); 3.84 (s, 2H); 3.52 (t, 2H); 2.75 (t, 2H); and showed the presence of approximately 1.2 moles of methanol.

Anal. Calcd for $C_9H_{14}N_8O_2S_3 \cdot 1.2CH_3OH$: C, 30.56; H, 4.72; N, 27.95; S, 23.99.

Found (corr. for 1.31% $H_2O$): C, 30.19; H, 4.32; N, 27.91; S, 24.71.

## Example 36

### 3-{2-[(2-Guanidinothiazol-4-yl)methylthio]ethylamino}-4-(2-hydroxyethylamino)-1,2,5-thiadiazole 1,1-dioxide

To a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.05 g; 11.5 mmoles) in 200 ml of dry methanol at 3° was added, dropwise over 30 minutes, a solution of 2-[(2-guanidinothiazol-4-yl)-methylthio]ethylamine (from the dihydrochloride; 3.5 g; 11.5 mmoles) in 40 ml of dry methanol. After 15 minutes at 3°, a solution of ethanolamine (1.03 ml, 17.3 mmoles) in 10 ml of methanol was rapidly added dropwise and stirred for 15 minutes. The reaction mixture was evaporated under reduced pressure to give the product as a friable foam that crystallized from methanol. Two recrystallizations from methanol yielded the title compound, mp = slowly resinified starting at 115°, decomposed starting at 175°.

Anal. Calcd for $C_{11}H_{18}N_8O_3S_3$: C, 32.50; H, 4.46; N, 27.57; S, 23.66.

Found (corr. for 3.85% $H_2O$): C, 32.77; H, 4.21; N, 27.90; S, 24.39.

Example 37

3-(2,3-Dihydroxypropylamino)-4-{2-[(2-guanidinothiazol-4-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

When a methanolic solution of 2-[(2-guanidinothiazol-4-yl)methylthio]ethylamine is reacted with 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide by the procedure of Example 31 and the resultant 3-methoxy-4-{2-[(2-guanidinothiazol-4-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide is treated with 3-amino-1,2-propanediol, the title compound is thereby produced.

Example 38

3-Methylamino-4-{2-[(thiazol-2-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

When a methanolic solution of 2-[(thiazol-2-yl)-methylthio]ethylamine [prepared according to the procedure described in U.S. Patent 3,950,333] is reacted with 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide and the resultant 3-methoxy-4-{2-[(thiazol-2-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide treated with methylamine according to the general procedure described in Example 31, the title compound is thereby produced.

Example 39

When 2-chloromethyl-4-methylthiazole [prepared by the reaction of thionyl chloride and 2-hydroxymethyl-4-methylthiazole, which itself is prepared according to the

procedure of J. Chem. Soc., (Suppl. Issue No. 1), S106-111 (1966). or Acta Chem. Scand., 20, 2649 (1966)] is reacted with cysteamine hydrochloride and about two equivalents of a strong base such as sodium methoxide, and the resultant amine is treated with 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide, there is produced 3-methoxy-4-{2-[(4-methylthiazol-2-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide. When the latter compound is reacted with methylamine according to the general procedure of Example 31, there is produced 3-methylamino-4-{2-[(4-methylthiazol-2-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide.

When the above procedure is repeated, except that the 2-chloromethyl-4-methylthiazole utilized therein is replaced by an equimolar amount of the chloromethylthiazoles prepared by reacting thionyl chloride with
2-amino-4-hydroxymethylthiazole[1],
2-hydroxymethyl-4,5-dimethylthiazole[2],
4-hydroxymethyl-2-methylthiazole[3],
4-hydroxymethyl-2-chlorothiazole[4],
5-hydroxymethyl-2-methylthiazole[5],
5-hydroxymethyl-4-methylthiazole[6],
4-hydroxymethylthiazole[7] and
4-dimethylaminomethyl-2-hydroxymethylthiazole[8], respectively, there is thereby produced
3-{2-[(2-aminothiazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(4,5-dimethylthiazol-2-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(2-methylthiazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,

3-{2-[(2-chlorothiazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide, 3-{2-[(2-methylthiazol-5-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide, 3-{2-[(4-methylthiazol-5-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide, 3-{2-[(thiazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide and 3-{2-[(4-dimethylaminomethylthiazol-2-yl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide, respectively.

The above starting materials are prepared according to the procedures described in the following publications:

(1) J. Am. Chem. Soc., 68, 2155 (1946);

(2) Helv. Chim. Acta, 31, 652 (1948);

(3) and (5) Zh. Obshch. Khim., 32, 570 (1962) [C. A., 58, 2525b (1963)];

(4) Rev. Roumaine Chim., 10, 897 (1965) [C. A., 64, 8164b (1966)];

(6) J. Am. Chem. Soc., 67, 400 (1945);

(7) Zh. Obshch. Khim., 27, 726 (1957) [C. A., 51, 16436h (1957)];

(8) An ethanol solution of dimethylamine is reacted with 2-bromo-4-chloromethylthiazole, prepared according to reference (4) above, and the resultant 2-bromo-4-dimethylaminomethylthiazole is treated with a strong base and formaldehyde according to the general procedure described in Acta Chem. Scand., 20, 2649 (1966), to give the desired 4-dimethylaminomethyl-2-hydroxymethyl-thiazole.

Example 40

3-{3-[(2-Dimethylaminomethyl-4-thiazolyl)methylthio]propyl-amino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

When 2-dimethylaminomethyl-4-hydroxymethylthiazole [prepared in Example 34, Step D] is reacted with 3-mercapto-propylamine hydrochloride [prepared according to the procedure described in J. Org. Chem., 27, 2846 (1962)] in aqueous hydrobromic acid (48%), and the resultant amine is successively treated with 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide and excess methylamine as in the general procedure of Example 31, the title compound is produced.

Example 41

3-{2-[(2-Guanidinothiazol-4-yl)methylthio]propylamino}-4-amino-1,2,5-thiadiazole 1-oxide

When a methanolic solution of 2-[(guanidinothiazol-4-yl)methylthio]propylamine is reacted with 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide [prepared in Example 4, Step A], and the resultant 3-{2-[(2-guanidinothiazol-4-yl)methyl-thio]propylamino}-4-methoxy-1,2,5-thiadiazole 1-oxide is treated with excess ammonia by the procedure in Example 35, the title compound is thereby produced.

Example 42

3-{2-[(2-Guanidinothiazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

Reaction of a methanolic suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide with one equivalent of methylamine and treatment of the resultant 3-methoxy-4-methylamino-1,2,5-thiadiazole 1,1-dioxide with one equivalent of 2-[(2-guanidinothiazol-4-yl)methylthio]ethylamine yields the title compound, which is identical to the product obtained in Example 31.

Example 43

3-{2-[(2-Guanidinothiazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

When a solution of 3-methylamino-4-(2-mercaptoethyl)-1,2,5-thiadiazole 1,1-dioxide [prepared in Example 25, Step A] is reacted with 4-chloromethyl-2-guanidinothiazole hydrochloride and a strong base, the title compound is thereby produced, which is identical to the product obtained in Example 31.

Example 44

3-{2-[(2-Guanidinothiazol-4-yl)methylthio]ethylamino}-4-hydroxy-1,2,5-thiadiazole 1,1-dioxide

When 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is reacted with one equivalent of 2-[(2-guanidinothiazol-4-yl)methylthio]ethylamine and the resultant 3-{2-[(2-guanidinothiazol-4-yl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide is reacted with sodium hydroxide according to the procedure described in Example 17, Step B, the title compound is produced.

Example 45

3-{2-[(2-Dimethylaminomethyl-4-thiazolyl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

Reaction of a methanolic suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide with one equivalent of methylamine and treatment of the resultant 3-methoxy-4-methylamino-1,2,5-thiadiazole 1,1-dioxide with one equivalent of 2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamine [prepared in Example 33, Step E], produces the title compound which is identical to the product prepared in Example 33.

Example 46

3-{2-[(2-Dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

Reaction of 3-methylamino-4-(2-mercaptoethyl)-1,2,5-thiadiazole 1,1-dioxide [prepared in Example 25, Step A] with about one equivalent of 2-dimethylaminomethyl-4-hydroxymethylthiazole [prepared in Example 34, Step D] in concentrated hydrochloric acid, and then made basic and worked up, produces the title compound which is identical to the product prepared in Example 33.

Example 47

3-{2-[(2-Dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-hydroxy-1,2,5-thiadiazole 1,1-dioxide

When a solution of 3-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide [prepared according to the procedure described in Example 33, Step F] is reacted with sodium hydroxide according to the procedure described in Example 17, Step B, the title compound is produced.

## Example 48

### 3-Amino-4-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-1,2,5-thiadiazole 1-oxide

When a methanolic solution of 3-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1-oxide [prepared from 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide by the general procedure described in Example 34, Step F] is reacted with anhydrous ammonia according to the general procedure described in Example 35, the title compound is thereby produced.

## Example 49

### 3-{2-[(2-Dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide

Reaction of 3-methylamino-4-(2-mercaptoethyl)-1,2,5-thiadiazole 1-oxide [prepared by reacting 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide with 2-aminoethanethiol and methylamine according to the procedure described in Example 25, Step A] with about one equivalent of 2-dimethylaminomethyl-4-hydroxymethylthiazole [prepared in Example 34, Step D], produces the title compound.

## Example 50

3-Amino-4-[4-(2-guanidinothiazol-4-yl)butylamino]-1,2,5-thiadiazole 1-oxide

When a methanolic solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide is successively treated with 4-(2-guanidinothiazol-4-yl)butylamine [prepared according to the procedure described in U.S. Patent 4,165,377] and excess anhydrous ammonia according to the general procedure described in Example 35, the title compound is thereby produced.

## Example 51

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-hydrazino-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamine (2.41 g; 11.2 mmoles) in 30 ml of dry methanol was added dropwise over a period of 45 minutes to a well stirred cold (ice-water bath) suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.0 g; 11.2 mmoles) in 250 ml of methanol. After stirring at 0° for 15 minutes, a solution of anhydrous hydrazine (1.8 g; 56.13 mmoles) in 30 ml of dry methanol was added all at once, and stirring was continued for 30 minutes. The reaction mixture was evaporated under reduced pressure and the solid residue was treated with chloroform and filtered to give 3.28 g of the title compound, mp 170° (dec.).

## Example 52

3-Methylamino-4-{2-[(2-pyridyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(2-pyridyl)methylthio]ethylamine (from the dihydrobromide, 3.5 g; 10.6 mmoles) [prepared according to the procedure described in Belgian Patent 779,775] in 25 ml of dry methanol was added dropwise over 30 minutes to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide in 200 ml of dry methanol that was cooled to 0-5° in an ice-water bath. After stirring the cold solution for 15 minutes, anhydrous methylamine was bubbled into the solution for 15 minutes. The reaction mixture was stirred at ambient temperature for 45 minutes, evaporated under reduced pressure and the residue crystallized with methanol. Two recrystallizations from methanol yielded the title compound, mp 168-171°.

Anal. Calcd for $C_{11}H_{15}N_5O_2S_2$: C, 42.15; H, 4.82; N, 22.35; S, 20.46.

Found: C, 42.07; H, 4.75; N, 22.28; S, 20.73.

## Example 53

3-{2-[(3-Chloro-2-pyridyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

When a methanolic solution of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is successively treated with 2-[(3-chloro-2-pyridyl)methylthio]ethylamine [prepared according

to the procedure described in U.S. Patent 4,024,260] and methylamine according to the general procedure of Example 52, the title compound is thereby produced.

Example 54

3-{2-[(6-Dimethylaminomethyl-2-pyridyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

When a methanolic solution of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is successively treated with an equimolar amount of 2-[(6-dimethylaminomethyl-2-pyridyl)methylthio]ethylamine [prepared in Example 136, Step C] and excess methylamine, the title compound is thereby produced.

Example 55

The general procedure of Example 52 is repeated except that the 2-[(2-pyridyl)methylthio]ethylamine utilized therein is replaced by an equimolar amount of
2-[(3-bromo-2-pyridyl)methylthio]ethylamine,
2-[(3-cyano-2-pyridyl)methylthio]ethylamine,
2-[(3-hydroxy-2-pyridyl)methylthio]ethylamine,
2-[(3-methoxy-2-pyridyl)methylthio]ethylamine,
2-[(3-ethoxy-2-pyridyl)methylthio]ethylamine,
2-[(3-methyl-2-pyridyl)methylthio]ethylamine and
2-[(3-amino-2-pyridyl)methylthio]ethylamine, respectively,

[prepared according to the general procedures described in Belgian Patents 779,775, 804,144 and 844,504] and there is thereby produced
3-{2-[(3-bromo-2-pyridyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(3-cyano-2-pyridyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(3-hydroxy-2-pyridyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(3-methoxy-2-pyridyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(3-ethoxy-2-pyridyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(3-methyl-2-pyridyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide and
3-{2-[(3-amino-2-pyridyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide, respectively.

Example 56

3-{2-[(3-Chloro-2-pyridyl)methylthio]ethylamino}-4-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

When a methanolic solution of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is successively treated with 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine and 2-[(3-chloro-2-pyridyl)methylthio]ethylamine, the title compound is thereby produced.

Example 57

3-{2-[(6-Dimethylaminomethyl-2-pyridyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide

When a methanolic solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide [obtained from Example 4, Step A] is successively treated with an equimolar amount of 2-[(6-dimethylaminomethyl-2-pyridyl)methylthio]ethylamine [prepared in Example 136, Step C] and an excess of methylamine, the title compound is thereby produced.

Example 58

3-{2-[(4-Methyl-1,2,5-oxadiazol-3-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A. 3-Hydroxymethyl-4-methylfurazan

To a stirred solution of 3-methyl-4-furazancarboxylic acid (27.0 g; 0.21 mole) in 180 ml of tetrahydrofuran (that was cooled in an ice-water bath) under a nitrogen atmosphere was added dropwise a 1.02M solution of borane in tetrahydrofuran (825 ml; 0.84 mole). When the addition was completed, the mixture was stirred at ambient temperature overnight. After 20 hours, 6N HCl was added dropwise until the evolution of hydrogen ceased and the reaction mixture was evaporated under reduced pressure. The residue was partitioned between methylene chloride and water, made basic with potassium carbonate and the combined methylene chloride

extract was dried and evaporated under reduced pressure to give 21.0 g of product. Vacuum distillation yielded the title compound, bp 99°/1 mm Hg.

B. 2-[(4-Methyl-1,2,5-oxadiazol-3-yl)methylthio]-ethylamine

A solution of 3-hydroxymethyl-4-methylfurazan (2.49 g; 21.8 mmoles) [prepared in Step A] and 2-amino-ethanethiol hydrochloride (2.48 g; 21.8 mmoles) in 60 ml of 48% aqueous hydrobromic acid was stirred and heated at reflux temperature for 23 hours and then at ambient temperature for 40 hours. The excess hydrobromic acid was removed under reduced pressure, and the oil residue was dissolved in isopropyl alcohol, filtered through Celite and the product was crystallized from the filtrate. Recrystallization from isopropyl alcohol yielded the title compound as the hydrobromide salt, mp 142-143°.

C. 3-{2-[(4-Methyl-1,2,5-oxadiazol-3-yl)methyl-thio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

When a methanolic suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is successively treated with an equimolar amount of 2-[(4-methyl-1,2,5-oxadiazol-3-yl)-methylthio]ethylamine [prepared in Step B] and excess methylamine by the general procedure of Example 2, the title compound is thereby produced.

Example 59

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-{2-[(4-methyl-1,2,5-oxadiazol-3-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

When a methanolic solution of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is treated with 2-[(4-methyl-1,2,5-oxadiazol-3-yl)methylthio]ethylamine [prepared in Example 58, Step B] and 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine, the title compound is thereby produced.

Example 60

3-{2-[(5-Methyl-1,2,4-oxadiazol-3-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A. 2-[(5-Methyl-1,2,4-oxadiazol-3-yl)methylthio]-ethylamine

Cysteamine hydrochloride (3.03 g; 26.7 mmoles) was added in several portions over a period of 10 minutes to a stirred solution of sodium methylate (2.89 g; 53.4 mmoles) in 50 ml of methanol at 0°. After stirring for 70 minutes at 0°, a solution of 3-chloromethyl-5-methyl-1,2,4-oxadiazole (3.54 g; 26.7 mmoles) in 15 ml of methanol was added dropwise over a period of 15 minutes, and the reaction mixture was allowed to stir at ambient temperature for 16 hours. The mixture was filtered, evaporated and redissolved in

isopropyl alcohol, then filtered and evaporated under reduced pressure to give the title compound (5.64 g) as a yellow oil. The NMR spectrum (60 MHz) in $CDCl_3$ gave the following resonances δ: 3.77 (s, 2H); 2.77 (m, 4H); 2.63 (s, 3H).

B. 3-{2-[(5-Methyl-1,2,4-oxadiazol-3-yl)-methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

When a methanolic suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is treated successively with 2-[(5-methyl-1,2,4-oxadiazol-3-yl)methylthio]ethylamine [prepared in Step A] and methylamine, by the general procedure of Example 2, the title compound is thereby produced.

Example 61

3-{2-[(2-Methyl-1,3,4-oxadiazol-5-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A. 2-[(2-Methyl-1,3,4-oxadiazol-5-yl)methylthio]-ethylamine

Cysteamine hydrochloride (1.13 g; 0.01 mole) was added to a stirred solution of sodium methylate (1.08 g; 0.02 mole) in 20 ml of methanol at 0° under an argon atmosphere. The mixture was stirred for 1 hour at 0° and the

resultant suspension was added dropwise over a period of 25 minutes to a stirred solution of 2-methyl-5-chloromethyl-1,3,4-oxadiazole (1.32 g; 0.01 mole) [prepared by the procedure described in Hel. Chim. Acta, 55, 1979 (1972)] in 15 ml of methanol at 0°. The reaction mixture was stirred at ambient temperature for 45 minutes, concentrated to near dryness, and then diluted with methylene chloride, filtered and evaporated under reduced pressure to give the title compound (1.92 g) as a yellow oil. The NMR spectrum (60 MHz) in $CDCl_3$ gave the following resonances δ: 3.87 (s, 2H); 2.8 (m, 4H); 2.53 (s, 3H).

B. 3-{2-[(2-Methyl-1,3,4-oxadiazol-5-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

When a suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is treated with an equimolar amount of 2-[(2-methyl-1,3,4-oxadiazol-5-yl)methylthio]ethylamine [prepared in Step A] and an excess of methylamine by the general procedure described in Example 2, the title compound is thereby produced.

## Example 62

3-{2-[(2-Dimethylamino-1,3,4-oxadiazol-5-yl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

When 2-dimethylamino-5-ethoxycarbonyl-1,3,4-oxadiazole [prepared according to the procedure described in Org. Magn. Resonance, 6, 144 (1974)] is hydrolyzed and reduced with borane as described in Example 58, Step A,

and then is reacted with cysteamine according to the procedure described in Example 60, Step A, there is produced 2-[(2-dimethylamino-1,3,4-oxadiazol-5-yl)methylthio]-ethylamine.

When the above amine is reacted with an equimolar amount of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide, and the resultant 3-{2-[(2-dimethylamino-1,3,4-oxadiazol-5-yl)-methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide is treated with an excess of methylamine, the title compound is thereby produced.

Example 63

3-{2-[(3-{Dimethylaminomethyl}phenyl)methylthio]ethyl-amino}-4-amino-1,2,5-thiadiazole 1,1-dioxide

When a methanolic suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is successively treated with an equimolar amount of 2-[(3-{dimethylaminomethyl}phenyl)-methylthio]ethylamine [prepared according to the procedure described in Belgian Patent 867,106] and excess ammonia by the general procedure described in Example 35, the title compound is thereby produced.

Example 64

3-{3-[3-(Dimethylaminomethyl)phenoxy]propylamino}-4-amino-1,2,5-thiadiazole 1,1-dioxide

When a methanolic suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is successively treated with an equimolar amount of 3-[3-(dimethylaminomethyl)phenoxy]-propylamine [prepared according to the procedure described in Belgian Patent 867,106] and excess ammonia by the general procedure described in Example 35, the title compound is thereby produced.

Example 65

3-{2-[(5-Dimethylaminomethyl-2-thienyl)methylthio]ethyl-amino}-4-methylamino-1,2,5-thiadiazole 1,I-dioxide

A solution of 2-[(5-dimethylaminomethyl-2-thienyl)-methylthio]ethylamine (1.0 g; 4.34 mmoles) [prepared according to the procedure described in Belgian Patent 867,105] in 25 ml of dry methanol was added dropwise over a period of 35 minutes to a stirred solution of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (0.77 g; 4.34 mmoles) in 150 ml of dry methanol that had been cooled to 0-3° in an ice-water bath. After the addition was completed, anhydrous methylamine was bubbled into the solution for 10 minutes and stirring was continued for 15 minutes. The reaction mixture was evaporated under reduced pressure and the residue placed on 50 g of silica gel and chromatographed using a gradient elution of acetonitrile-methanol. The appropriate fractions were combined to give 1.0 g of product. Recrystallization from methanol yielded the title compound, mp 60.5-66°.

Example 66

3-{2-[(5-Dimethylaminomethyl-2-thienyl)methylthio]ethylamino}-4-ethylamino-1,2,5-thiadiazole 1-oxide

When a solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide [prepared in Example 4, Step A] is successively reacted with an equimolar amount of 2-[(5-dimethylaminomethyl-2-thienyl)methylthio]ethylamine and excess ethylamine according to the procedure described in Example 18, the title compound is thereby produced.

Example 67

3-{2-[(5-Dimethylaminomethyl-2-thienyl)methylthio]ethylamino}-4-{2-[(4-methyl-1,2,5-oxadiazol-3-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

When a suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is reacted with an equimolar amount of 2-[(5-dimethylaminomethyl-2-thienyl)methylthio]ethylamine and the resultant 3-{2-[(5-dimethylaminomethyl-2-thienyl)-methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide is treated with 2-[(4-methyl-1,2,5-oxadiazol-3-yl)-methylthio]ethylamine [prepared in Example 58, Step B], the title compound is thereby produced.

Example 68

3-{4-[(2-Guanidino-4-oxazolyl]butylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

When a suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is reacted with an equimolar amount of 4-[(2-guanidino-4-oxazolyl]butylamine [prepared according to the procedure described in Belgian Patent 866,155] and the resultant 3-{4-[(2-guanidino-4-oxazolyl]-butylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide is treated with excess methylamine, the title compound is thereby produced.

Example 69

3-{2-[(2-(2-Amino-5-oxazolyl)ethylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

Reacting an equimolar amount of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide and 2-[2-(2-amino-5-oxazolyl)ethylthio]ethylamine [prepared according to U.S. Patent 3,950,353] and treatment of the resultant 3-{2-[2-(2-amino-5-oxazolyl)ethylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide with excess methylamine gives the title compound.

## Example 70

3-{2-[3-Isoxazolylmethylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

Reaction of a methanolic suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide with one equivalent of 2-[3-isoxazolylmethylthio]ethylamine [prepared according to the procedure described in U.S. Patent 3,950,353] and treatment of the resultant 3-{2-[3-isoxazolylmethylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide with an excess of methylamine, produced the title compound.

## Example 71

The general procedure of Example 70 is repeated except that the 2-[3-isoxazolylmethylthio]ethylamine utilized therein is replaced by an equimolar amount of 2-[(5-methyl-3-isoxazolyl)methylthio]ethylamine, 2-[(3,5-dimethyl-4-isoxazolyl)methylthio]ethylamine and 2-[(2-(5-methyl-4-isoxazolyl)ethylthio]ethylamine, respectively, [each prepared by the general procedure described in U.S. Patent 3,950,353] and there is thereby produced 3-{2-[(5-methyl-3-isoxazolyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide, 3-{2-[(3,5-dimethyl-4-isoxazolyl)methylthio}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide and 3-{2-[2-(5-methyl-4-isoxazolyl)ethylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide, respectively.

Example 74

The general procedure of Example 73 is repeated except that the 2-[3-isothiazolylmethylthio]ethylamine utilized therein is replaced by an equimolar amount of 2-[(3-methyl-4-isothiazolyl)methylthio]ethylamine, 2-[(4-bromo-3-methyl-5-isothiazolyl)methylthio]ethylamine and 2-[(3-methyl-5-isothiazolyl)methylthio]ethylamine, respectively, [prepared by the general procedures described in U.S. Patent 3,450,353 and J. Chem. Soc., 2032 (1963)] and there is thereby produced 3-{2-[(3-methyl-4-isothiazolyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide, 3-{2-[(4-bromo-3-methyl-5-isothiazolyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide and 3-{2-[(3-methyl-5-isothiazolyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide, respectively.

Example 75

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-{2-[3-isothiazolylmethylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

When a methanol suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is reacted with one equivalent of 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine according to the procedure described in Example 17, Step A,

under reduced pressure. The residue was dissolved in 80 ml of 3N HCl and extracted with ether. The aqueous phase was adjusted to pH 8 and extracted with methylene chloride. The organic phase was dried, filtered and evaporated under vacuum to give 6.0 g of the title compound as an oil. The NMR spectrum (60 MHz) in $CDCl_3$ gave the following resonances δ: 7.50 (s, 1H); 4.85 (s, 2H); 4.15 (s, 1H); 3.75 (s, 2H); 2.35 (s, 6H).

C. 2-Chloromethyl-5-dimethylaminomethylthiazole hydrochloride

Thionyl chloride (27.4 g; 0.16 moles) was added dropwise to a cooled (ice-water bath) solution of 5-hydroxymethyl-2-dimethylaminomethylthiazole (8.9 g; 52.0 mmoles) [prepared in Step B] in 300 ml of methylene chloride. The mixture was heated at reflux temperature for 2 hours and then cooled and evaporated under reduced pressure to give 12.3 g of product. Crystallization from acetonitrile yielded the title compound, mp 143-144°.

Anal. Calcd for $C_7H_{12}Cl_2N_2S$: C, 37.01; H, 5.32; N, 12.33; Cl, 31.63.

Found (corr. for 0.91% $H_2O$): C, 36.88; H, 5.11; N, 12.14; Cl, 31.65.

D. 2-[(2-Dimethylaminomethylthiazol-5-yl)-methylthio]ethylamine

Cysteamine hydrochloride (0.2 g; 1.76 mmoles) and 5-chloromethyl-2-dimethylaminomethylthiazole hydrochloride (0.4 g; 1.76 mmoles) [prepared in Step C] were dissolved in 2.5 ml of concentrated hydrochloric acid and the solution was heated at an oil bath temperature of 100°. After 2 hours, the mixture was evaporated under reduced

Example 72

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-{2-[3-isoxazolylmethylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

When a methanolic suspension of 3,4-dimethoxy-1,2,5,thiadiazole 1,1-dioxide is reacted with one equivalent of 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine according to the procedure described in Example 17, Step A, and the resultant product is treated with one equivalent of 2-[(3-isoxazolylmethylthio]ethylamine, the title compound is thereby produced.

Example 73

3-{2-[3-Isothiazolylmethylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

Reaction of a methanol suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide with one equivalent of 2-[3-isothiazolylmethylthio]ethylamine [prepared according to the procedure described in U.S. Patent 3,950,353] and treatment of the resultant 3-{2-[3-isothiazolylmethylthio]-ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide with an excess of methylamine, produces the title compound.

and the resultant 3-{2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide is treated with one equivalent of 2-[3-isothiazolylmethylthio]ethylamine, the title compound is produced.

Example 76

3-{2-[(2-Amino-1,3,4-thiadiazol-5-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

Reaction of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide with one equivalent of 2-[(2-amino-1,3,4-thiadiazol-5-yl)methylthio]ethylamine [prepared according to the procedure described in U.S. Patent 3,950,353] and treatment of the resultant 3-{2-[(2-amino-1,3,4-thiadiazol-5-yl)-methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide with methylamine, produced the title compound.

Example 77

The general procedure of Example 76 is repeated except that the 2-[(2-amino-1,3,4-thiadiazol-5-yl)methylthio]ethylamine utilized therein is replaced by an equimolar amount of
3-[1,2,4-thiadiazol-3-ylthio]propylamine,
2-[(1,2,3-thiadiazol-4-yl)methylthio]ethylamine,
2-[(3-hydroxy-1,2,5-thiadiazol-4-yl)methylthio]ethylamine and
2-[(3-amino-1,2,5-thiadiazol-4-yl)methylthio]ethylamine, respectively, [prepared by the general procedures described in U.S. Patent 3,950,353, J. Am. Chem. Soc., 86, 2861 (1964) and J. Org. Chem., 28, 1491 (1963)] and there is thereby produced

3-{3-[1,2,4-thiadiazol-3-ylthio]propylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(1,2,3-thiadiazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(3-hydroxy-1,2,5-thiadiazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide and
3-{2-[(3-amino-1,2,5-thiadiazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
respectively.

Example 78

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-{2-[(3-hydroxy-1,2,5-thiadiazol-4-yl)methylthio]-ethylamino}-1,2,5-thiadiazole 1,1-dioxide

When a methanol suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is reacted with an equimolar amount of 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine according to the procedure described in Example 17, Step A, and an equimolar amount of 2-[(3-hydroxy-1,2,5-thiadiazol-4-yl)methylthio]ethylamine, the title compound is thereby produced.

Example 79

3-{2-[(2-Amino-1,2,4-triazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

Reaction of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide with one equivalent of 2-[(2-amino-1,2,4-triazol-5-yl)methylthio]ethylamine [prepared according to general procedures described in U.S. Patent 3,950,353] and an excess of methylamine by the general procedure described in Example 2, produces the title compound.

Example 80

The general procedure of Example 79 is repeated except that the 2-[(2-amino-1,2,4-triazol-5-yl)methylthio]-ethylamine utilized therein is replaced by an equimolar amount of
2-[(4-methyl-1,2,4-triazol-3-yl)methylthio]ethylamine,
2-[(5-methyl-1,2,3-triazol-4-yl)methylthio]ethylamine and
2-[1,2,4-triazol-3-yl)methylthio]ethylamine, respectively, [each prepared by the general procedures described in U.S. Patent 3,950,353] and there is thereby produced
3-{2-[(4-methyl-1,2,4-triazol-3-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide,
3-{2-[(5-methyl-1,2,3-triazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide and
3-methylamino-4-{2-[1,2,4-triazol-3-ylmethylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide, respectively.

Example 81

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-{2-[(5-methyl-1,2,3-triazol-4-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

When a methanolic suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is reacted with an equimolar amount of 2-[(5-dimethylaminomethyl-2-furyl)methylthio]-ethylamine according to the procedure described in Example 17, Step A, and an equimolar amount of 2-[(5-methyl-1,2,3-triazol-4-yl)methylthio]ethylamine, the title compound is produced.

Example 82

3-{2-[(2-Dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-dimethylamino-1,2,5-thiadiazole 1-oxide

When a solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide [prepared in Example 4, Step A] is reacted with one equivalent of 2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamine [prepared in Example 33, Step E] and the resultant 3-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1-oxide is treated with an excess of dimethylamine according to the procedure described in Example 28, the title compound is thereby produced.

Example 83

The general procedure of Example 82 is repeated, except that the dimethylamine utilized therein is replaced by
pyrrolidine,
piperidine,
morpholine,
thiomorpholine,
piperazine,
N-acetylpiperazine,
N-methylpiperazine,
hexamethyleneimine and
homopiperazine, respectively,

and there is thereby produced
3-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-(1-pyrrolidinyl)-1,2,5-thiadiazole 1-oxide,
3-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-(1-piperidinyl)-1,2,5-thiadiazole 1-oxide,
3-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-(morpholinyl)-1,2,5-thiadiazole 1-oxide,
3-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-(4-thiomorpholinyl)-1,2,5-thiadiazole 1-oxide,
3-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-(1-piperazinyl)-1,2,5-thiadiazole 1-oxide,
3-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-(4-acetyl-1-piperazinyl)-1,2,5-thiadiazole 1-oxide,
3-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-(4-methyl-1-piperazinyl)-1,2,5-thiadiazole 1-oxide,
3-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-(1-hexamethyleneimino)-1,2,5-thiadiazole 1-oxide
and
3-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamino}-4-(1-homopiperazinyl)-1,2,5-thiadiazole 1-oxide,
respectively.

## Example 84

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-ethylamino-1,2,5-thiadiazole 1-oxide

A solution of 2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamine (2.64 g; 12.3 mmoles) in 25 ml of dry

methanol was added dropwise over a period of 30 minutes to a well stirred solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (2.0 g; 12.3 mmoles) in 75 ml of dry methanol that had been cooled to 8° in an ice-water bath. After 15 minutes, 4.0 ml of ethylamine was added and the mixture stirred at ambient temperature for 1 hour. The reaction mixture was evaporated under reduced pressure and the residue placed on 55 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined, evaporated under reduced pressure and the residue treated with ether and decanted. The residue was treated with fresh ether to give 1.5 g of the title compound, mp 68-74°.

Anal. Calcd. for $C_{14}H_{23}N_5O_2S_2$: C, 47.04; H, 6.48; N, 19.59; S, 17.94.

Found (corr. for 1.24% $H_2O$): C, 46.54; H, 6.33; N, 19.37; S, 17.96.

## Example 85

### 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-propylamino-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamine (2.41 g; 11.2 mmoles) in 25 ml of dry methanol was added dropwise over a period of 30 minutes to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.0 g; 11.2 mmoles) in 200 ml of dry methanol that had been cooled to 2° in an ice-water bath. After 15 minutes, 4.0 ml of n-propylamine was added all at once and the mixture stirred at ambient temperature for 30 minutes. The reaction mixture was evaporated under

reduced pressure and the residue placed on 55 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined, evaporated under reduced pressure and the syrup crystallized with ether to give 3.7 g of the title compound, mp 164-166°; the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the presence of approximately 0.9 moles of methanol.

Anal. Calcd for $C_{15}H_{25}N_5O_3S_2 \cdot 0.9CH_4O$: C, 45.86; H, 6.92; N, 16.82; S, 15.40.

Found: C, 45.60; H, 6.93; N, 17.03; S, 15.47.

## Example 86

### 3-Amino-4-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]-ethylamino}-1,2,5-thiadiazole 1-oxide

A solution of 2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamine (3.3 g; 15.4 mmoles) in 25 ml. of methanol was added dropwise over a period of 30 minutes to a well stirred solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (2.5 g; 15.4 mmoles) in 75 ml of methanol that had been cooled to 8° in an ice-water bath. After 1.5 hours, anhydrous ammonia was bubbled into the solution for 8 minutes and the mixture stirred at ambient temperature for 30 minutes. The reaction mixture was evaporated under reduced pressure and the residue placed on 60 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined and evaporated, and the product was crystallized from

acetonitrile. Recrystallization from isopropyl alcohol yielded 2.59 g of the title compound, mp 139-142°.

Anal. Calcd for $C_{12}H_{19}N_5O_2S_2$: C, 43.75; H, 5.81; N, 21.26; S, 19.46.

Found: C, 43.71; H, 6.05; N, 21.32; S, 19.51.

## Example 87

### 3-Amino-4-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]-ethylamino}-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine (2.5 g; 11.7 mmoles) in 50 ml. of dry methanol was added dropwise over 45 minutes to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.08 g; 11.8 mmoles) in 200 ml. of dry methanol that had been cooled to 5° in an ice-water bath. After 30 minutes, anhydrous ammonia was bubbled into the solution for 10 minutes and the mixture stirred at ambient temperature for 8 hours. The reaction mixture was evaporated under reduced pressure and the residue placed on 200 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined and evaporated to give 3.6 g of product. Recrystallization from methanol-ether yielded the title compound, mp 156-158°.

Anal. Calcd for $C_{12}H_{19}N_5O_3S_2$: C, 41.72; H, 5.54; N, 20.28; S, 18.56.

Found: C, 41.50; H, 5.52; N, 20.33; S, 18.74.

Example 88

3-Amino-4-{2-[(2-guanidinothiazol-4-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1-oxide

A solution of 2-[(guanidinothiazol-4-yl)methylthio]-ethylamine (from the dihydrochloride, 6.08 g; 20.0 mmoles) in 50 ml of methanol was added dropwise, over 45 minutes, to a cold (5°) well stirred solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (3.24 g; 20.0 mmoles) in 150 ml of methanol. After stirring at 5-10° for 1.5 hours, anhydrous ammonia was bubbled into the solution for 10 minutes and stirring was continued at ambient temperature for 18 hours. The reaction mixture was evaporated under reduced pressure and the residue placed on 65 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined and evaporated to give 4.16 g of product from methanol. Recrystallization from methanol yielded the title compound, mp 167-170° (dec).

Anal. Calcd for $C_9H_{14}N_8OS_3$: C, 31.20; H, 4.07; N, 32.35; S, 27.76.

Found (corr. for 0.48% $H_2O$): C, 30.39; H, 3.97; N, 32.25; S, 27.91.

Recrystallization of the crude product from 95% ethanol yielded the title compound as a monohydrate, mp 136-138° (dec).

Anal. Calcd for $C_9H_{14}N_8OS_3 \cdot H_2O$: C, 29.66; H, 4.42; N, 30.75; S, 26.39.

Found: C, 29.92; H, 4.42; N, 30.84; S, 26.58.

A sample of the product as the free base was

suspended in 95% ethanol, treated with one equivalent of aqueous 6.0N hydrochloric acid and filtered to yield the hydrochloride salt, mp 200-201°C (dec.)

Anal. Calcd for $C_9H_{15}ClN_8OS_3$: C, 28.23; H, 3.95; N, 29.26; Cl, 9.26

Found (corr. for 1.02% $H_2O$): C, 28.26; H, 3.83; N, 29.41; Cl, 9.53

## Example 89

### 3-Benzylamino-4-{2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamine (2.4 g; 11.2 mmoles) in 30 ml of dry methanol was added dropwise over a period of 35 minutes to a stirred solution of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.0 g; 11.2 mmoles) in 200 ml of dry methanol that had been cooled to 1-3° in an ice water bath. After 15 minutes at 1-3°, benzylamine (1.8 g, 1.83 ml; 16.8 mmoles) was added and the solution stirred at ambient temperature for 1 hour. The reaction mixture was evaporated under reduced pressure and the residue placed on 50 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined to give 4.1 g of product. Recrystallization from aqueous methanol and then methanol yielded the title compound, mp 152° (dec); the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the presence of approximately 1.0 mole of methanol.

Anal. Calcd for $C_{19}H_{25}N_5O_3S_2 \cdot CH_4O$: C, 51.37; H, 6.25; N, 14.98.

Found: C, 51.51; H, 6.05; N, 14.78.

Example 90

3-{2-[(3-{Dimethylaminomethyl}phenyl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(3-{dimethylaminomethyl}phenyl)-methylthio]ethylamine (2.51 g; 11.2 mmoles) [prepared according to the procedure described in Belgian Patent 867,106] in 25 ml of dry methanol was added dropwise over 30 minutes to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.0 g; 11.2 mmoles) in 200 ml of dry methanol that had been cooled to 2° in an ice-water bath. After 15 minutes at 2-5°, anhydrous methylamine was bubbled into the solution for 10 minutes and the solution was then stirred at ambient temperature for 30 minutes. The reaction mixture was evaporated under reduced pressure and the residue placed on 60 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined to give 2.96 g of product. Recrystallization from acetonitrile and then from methanol yielded the title compound, mp 152-158°; the NMR spectrum (100 mHz) in $d_6$ dimethyl sulfoxide showed the presence of approximately 0.6 mole of methanol.

Anal. Calcd for $C_{15}H_{23}N_5O_2S_2 \cdot 0.6\ CH_4O$: C, 48.20; H, 6.59; N, 18.02; S, 16.49.

Found: C, 47.99; H, 6.78; N, 17.81; S, 16.09.

Example 91

3-Amino-4-{2-[(3-{dimethylaminomethyl}phenyl)methylthio]-ethylamino}-1,2,5-thiadiazole 1-oxide

A solution of 2-[(3-{dimethylaminomethyl}phenyl)-methylthio]ethylamine (2.77 g; 12.3 mmoles) in 25 ml of dry methanol was added dropwise over 45 minutes to a well stirred solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (2.0 g; 12.3 mmoles) in 100 ml of dry methanol that had been cooled to 5° in an ice-water bath. When the addition was completed, the solution was stirred at ambient temperature for 1.5 hours and then cooled to 5° and anhydrous ammonia was bubbled into the solution for 8 minutes. After stirring 16 hours at ambient temperature, the reaction mixture was evaporated under reduced pressure and the residue placed on 55 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined to give 3.0 g of product from acetonitrile. Recrystallization from acetone yielded the title compound, mp 122-125°.

Anal. Calcd for $C_{14}H_{21}N_5OS_2$: C, 49.53; H, 6.23; N, 20.63; S, 18.89.

Found: C, 49.18; H, 6.08; N, 20.93; S, 19.25.

## Example 92

### 3-{2-[(5-Dimethylaminomethyl-2-thienyl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide

A solution of 2-[(5-dimethylaminomethyl-2-thienyl)methylthio]ethylamine (1.5 g; 6.5 mmoles) in 25 ml of dry methanol was added dropwise over a period of 45 minutes to a stirred solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (1.06 g; 6.5 mmoles) in 150 ml of dry methanol that had been cooled to 3° in an ice-water bath. After 15 minutes at 3°, anhydrous methylamine was bubbled into the solution for 5 minutes and the solution

was stirred for 15 minutes. The reaction mixture, after standing overnight at ambient temperature, was evaporated under reduced pressure and the residue placed on 75 g of silica gel and chromatographed using a gradient elution of acetonitrile-methanol. The appropriate fractions were combined to give crystalline product from acetonitrile. Recrystallization from acetonitrile yielded the title compound, mp 98.5-102°.

Anal. Calcd for $C_{13}H_{21}N_5OS_3$: C, 43.42; H, 5.89; N, 19.48; S, 26.76.

Found: C, 43.70; H, 5.58; N, 19.71; S, 26.79.

## Example 93

### 3-Amino-4-{4-(5-dimethylaminomethyl-2-furyl)butylamino}-1,2,5-thiadiazole 1,1-dioxide

A solution of 4-(5-dimethylaminomethyl-2-furyl)-butylamine (1.61 g; 8.2 mmoles) in 25 ml of dry methanol was added dropwise over a period of 35 minutes to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (1.46 g; 8.2 mmoles) in 150 ml of dry methanol that had been cooled to 0-3° in an ice-water bath. After 15 minutes, anhydrous ammonia was bubbled into the solution for 5 minutes and the solution was stirred for 30 minutes. The reaction mixture was evaporated under reduced pressure and the residue placed on 60 g of silica gel and chromatographed using a gradient elution of acetonitrile-methanol. The appropriate fractions were combined and evaporated to give 1.68 g of product. Crystallization from acetonitrile yielded the title compound, mp 154-156° (dec).

Anal. Calcd for $C_{13}H_{21}N_5O_3S$: C, 47.69; H, 6.47; N, 21.39; S, 9.80.
Found: C, 47.73; H, 6.28; N, 21.43; S, 9.84.

## Example 94

### 3-Amino-4-{2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]-ethylamino}-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamine (0.9 g; 3.89 mmoles) in 20 ml of dry methanol was added dropwise over 40 minutes to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (0.69 g; 3.89 mmoles) in 70 ml of methanol that had been cooled to 8°, anhydrous ammonia was bubbled into the solution for 8 minutes and then the solution was allowed to stir at ambient temperature for 18 hours. The reaction mixture was evaporated under reduced pressure and the residue placed on 150 g of silica gel and chromatographed using a gradient elution of acetonitrile-methanol. The appropriate fractions were combined and evaporated to give 0.66 g of the product. The foam was dissolved in 2-propanol and evaporated to dryness to give the title compound, mp 60-65°; the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the presence of approximately 0.15 mole of 2-propanol.

Anal. Calcd for $C_{11}H_{18}N_6S_3O_2 \cdot 0.15C_3H_8O$: C, 37.02; H, 5.21; N, 22.62; S, 25.89.
Found (corr. for 2.79% $H_2O$) : C, 36.75; H, 5.13; N, 21.75; S, 25.03.

## Example 95

3-{2-[(2-Guanidinothiazol-5-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

(A) Ethyl 2-Guanidino-5-thiazolecarboxylate Hydrochloride

A solution of amidinothiourea (117 g; 0.99 mole) and ethyl chloro-α-formylacetate (150 g; 1.0 mole) in 3.5 liters of absolute ethanol was stirred at ambient temperature for 18 hours and then heated at reflux temperature for 1 hour. At this time additional ethyl chloro-α-formylacetate (20.0 g; 0.13 mole) was added and 1 hour later another 20.0 g of ethyl chloro-α-formylacetate was added. After 2 hours of additional heating at reflux temperature, the reaction mixture was evaporated under reduced pressure and the residue triturated with 1.5 liters of acetone and filtered to give 103 g of product. Recrystallization from 2-propanol yielded the title compound, mp 204-206°.

Anal. Calcd for $C_7H_{11}ClN_4O_2S$: C, 33.53; H, 4.43; N, 22.35; Cl, 14.14; S, 12.79.
Found: C, 33.38; H, 4.40; N, 22.54; Cl, 13.97; S, 12.92.

(B) 2-Guanidino-5-hydroxymethylthiazole

Ethyl 2-guanidino-5-thiazolecarboxylate hydrochloride (1.0 g; 3.99 mmoles) [prepared in Step A] was added to a cooled (ice-water bath) suspension of lithium aluminum hydride (0.46 g; 12.1 mmoles) in 25 ml of tetrahydrofuran. The reaction mixture was then heated at reflux temperature for 2 hours, cooled, decomposed with 0.46 ml

$H_2O$, 0.46 ml of 15% NaOH and 1.38 ml $H_2O$ and filtered. The filtrate was dried and evaporated under reduced pressure to give 0.61 g of product. Recrystallization from acetonitrile yielded the title compound, mp 168-170°.

Anal. Calcd for $C_5H_8N_4OS$: C, 34.87; H, 4.68; N, 32.54; S, 18.62.

Found: C, 34.55; H, 4.52; N, 32.63; S, 18.54.

(C) 2-[(2-Guanidinothiazol-5-yl)methylthio]-ethylamine

Cysteamine hydrochloride (10.6 g; 9.3 mmoles) and 2-guanidino-5-hydroxymethylthiazole (16.0 g; 9.3 mmoles) [prepared in Step B] were dissolved in 80 ml of concentrated hydrochloric acid and the solution stirred at ambient temperature for 1 hour and then heated at reflux temperature for 3 hours. The reaction mixture was cooled, made basic (pH 11) with 40% aqueous NaOH and filtered to give 15 g of product. Recrystallization from acetonitrile yielded the title compound, mp 150-153°.

Anal. Calcd for $C_7H_{13}N_5S_2$: C, 36.34; H, 5.66; N, 30.27; S, 27.72.

Found: C, 36.29; H, 5.70; N, 30.40; S, 27.64.

(D) 3-{2-[(2-Guanidinothiazol-5-yl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(2-guanidinothiazol-5-yl)-methylthio]ethylamine (2.0 g; 8.64 mmoles) [prepared in Step C] in 60 ml of methanol was added dropwise over 40 minutes to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (1.54 g; 8.64 mmoles) in

160 ml of methanol that had been cooled to 8° in an ice-water bath. While maintaining the temperature at 8°, anhydrous methylamine was bubbled into the solution for 8 minutes. After stirring at ambient temperature for 18 hours, the reaction mixture was evaporated under reduced pressure and the residue placed on 175 g of silica gel and chromatographed using a gradient elution of acetonitrile-methanol. The appropriate fractions were combined to give 1.3 g of product. Recrystallization from methanol yielded the title compound, mp 225-226° (dec).

Anal. Calcd for $C_{10}H_{16}N_8O_2S_3$: C, 31.90; H, 4.28; N, 29.76; S, 25.55.

Found: C, 32.07; H, 4.14; N, 29.91; S, 25.60.

## Example 96

### 3-Amino-4-{2-[(2-guanidinothiazol-5-yl)methylthio]-ethylamino}-1,2,5-thiadiazole 1-oxide

A solution of 2-[(2-guanidinothiazol-5-yl)-methylthio]ethylamine (3.0 g; 13.0 mmoles) [prepared in Example 95, Step C] in 70 ml of methanol was added dropwise over 40 minutes to a well stirred solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (2.1 g; 13.0 mmoles) in 200 ml of methanol that had been cooled to 8°, and anhydrous ammonia was then bubbled into the solution for 8 minutes. After stirring at ambient temperature for 18 hours, the reaction mixture was evaporated under reduced pressure and the residue placed on 225 g of silica gel and chromatographed using a gradient elution of acetonitrile-methanol. The appropriate fractions were combined to give 3.6 g of the title compound, mp 85-132°; the NMR spectrum (100 MHz) in

$d_6$ dimethyl sulfoxide showed the presence of approximately 0.3 mole of acetonitrile.

Anal. Calcd for $C_9H_{14}N_8OS_3 \cdot 0.3C_2H_3N$: C, 32.24; H, 4.22; N, 32.41; S, 26.71.

Found (corr. for 1.84% $H_2O$) : C, 32.63; H, 4.33; N, 32.55; S, 26.62.

## Example 97

3-Cyclopropylamino-4-{2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 13 was repeated, except that the 2-propynylamine utilized therein was replaced by an equimolar amount of cyclopropylamine, and the product was crystallized from methanol. Recrystallization from isopropyl alcohol yielded 3.5 g of the title compound, mp 194-195° (dec.); the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide and showed the presence of approximately 1.0 mole of isopropyl alcohol.

Anal. Calcd for $C_{15}H_{23}N_5O_3S_2 \cdot C_3H_8O$: C, 48.52; H, 7.01; N, 15.72.

Found: C, 48.36; H, 6.95; N, 14.87.

## Example 98

3-Cyclopropylmethylamino-4-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 13 was repeated,

except that the 2-propynylamine utilized therein was replaced by an equimolar amount of cyclopropylmethyamine, and the product was crystallized from methanol. Recrystallization from methanol yielded 1.6 g of the title compound, mp 86-89° (dec.); the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the presence of approximately 1.25 moles of methanol.

Anal. Calcd for $C_{16}H_{25}N_5O_3S_2 \cdot 1.25\ CH_4O$: C, 47.13, H, 6.88; N, 15.93.

Found (corr. for 0.68% $H_2O$): C, 47.40; H, 6.49; N, 15.77.

## Example 99

### 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-morpholino-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 28 was repeated, except that the dimethylamine utilized therein was replaced by an equimolar amount of morpholine. After column chromatography, the product was crystallized from isopropyl alcohol. The mixture was diluted with Skellysolve B and filtered to yield the title compound, mp 122-127°.

Anal. Calcd for $C_{16}H_{25}N_5O_4S_2$: C, 46.24; H, 6.06; N, 16.86.

Found (corr. for 0.61% $H_2O$): C, 45.82; H, 6.06; N, 16.62.

## Example 100

### 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-(2-methoxyethylamino)-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 13 was repeated, except that the 2-propynylamine utilized therein was

replaced by an equimolar amount of 2-methoxyethylamine. After column chromatography, the residue was treated with isopropyl alcohol, evaporated to near dryness and cooled to give 3.79 g of product. Recrystallization from isopropyl alcohol yielded the title compound, mp 56-58°; the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the presence of approximately 0.6 moles of isopropyl alcohol.

Anal. Calcd for $C_{15}H_{25}N_5O_4S_2 \cdot 0.6\ C_3H_8O$: C, 45.90; H, 6.83; N, 15.93.

Found (corr. for 0.74% $H_2O$): C, 45.50; H, 6.72; N, 15.63.

## Example 101

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-pyrrolidino-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 28 was repeated, except that the dimethylamine utilized therein was replaced by an equimolar amount of pyrrolidine. The crude reaction mixture was evaporated under reduced pressure, treated with isopropyl alcohol and filtered to yield 3.9 g of the title compound, mp 151-152°.

Anal. Calcd for $C_{16}H_{25}N_5O_3S_2$: C, 48.09; H, 6.31; N, 17.53.

Found: C, 48.00; H, 6.10; N, 17.71.

## Example 102

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]-ethylamino}-4-piperidino-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 28 was repeated, except that the dimethylamine utilized therein was replaced

by an equimolar amount of piperidine. Chromatography yielded 3.8 g of product. Recrystallization from hot aqueous ethanol yielded the title compound, mp 106-108°.
Anal. Calcd. for $C_{18}H_{27}N_5O_3S_2$: C, 49.37; H, 6.58; N, 16.94.

Found (corr. for 0.2% $H_2O$): C, 49.17; H, 6.52; N, 17.14.

Example 103

3-Butylamino-4-{2-[(5-dimethylaminomethyl-2-furyl)methylthio]-ethylamino}-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 13 was repeated, except that the 2-propynylamine utilized therein was replaced by an equimolar amount of butylamine. The crude product was chromatographed three times and dried with heating under high vacuum for 3.5 hours to yield 1.81 g of the title compound as a somewhat gummy foam.
Anal. Calcd for $C_{16}H_{27}N_5O_3S_2$: C, 47.86; H, 6.78; N, 17.44.

Found (corr. for 1.34% $H_2O$): C, 47.60; H, 6.81; N, 17.81.

Example 104

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-[(2-pyridyl)methylamino]-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 13 was repeated, except that the 2-propynylamine utilized therein was replaced by an equimolar amount of 2-aminomethylpyridine. The appropriate fractions from column chromatography were combined to give 3.9 g of product. Two recrystallizations from isopropyl alcohol yielded the title compound, mp 43-45°. A sample was recrystallized from absolute ethanol and

the solid was heated under vacuum at 60° for 6 hours to give a melt. The melt was dissolved in hot isopropyl alcohol, collected by filtration at ambient temperature and dried under high vacuum to yield the title compound, mp 45-47°; the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the presence of approximately 1.25 moles of isopropyl alcohol.

Anal. Calcd for $C_{18}H_{24}N_6O_3S_2 \cdot 1.25\ C_3H_8O$: C, 51.05; H, 6.70; N, 16.42.

Found (corr. for 0.58% $H_2O$): C, 51.08; H, 6.32; N, 16.03.

## Example 105

### 3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-hydroxylamino-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 13 was repeated, except that the 2-propynylamine utilized therein was replaced by an equimolar amount of hydroxylamine. The crude reaction mixture which had deposited the product as an oil was heated to reflux temperature until all the product crystallized, then filtered and dried to give 2.59 g of the title compound, mp 203-205°.

Anal. Calcd for $C_{12}H_{19}N_5O_4S_2$: C, 39.87; H, 5.30; N, 19.38; S, 17.74.

Found (corr. for 1.18% $H_2O$): C, 39.53; H, 5.04; N, 19.61; S, 17.62.

Example 106

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-dodecylamino-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamine (2.41 g; 11.2 mmoles) in 25 ml of methanol was added dropwise to a well stirred cold suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.0 g; 11.2 mmoles) in 200 ml of methanol. After stirring at 2-5° for 15 minutes, a solution of dodecylamine (4.15 g; 22.4 mmoles) in 25 ml of methanol was added all at once, and stirring was continued at ambient temperature for 18 hours. The reaction mixture was filtered and evaporated under reduced pressure, and the residue placed on 60 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined, evaporated and the residue was rechromatographed on 60 g of silica gel using a gradient elution of acetonitrile-methanol. The appropriate fractions from the second chromatography were combined, concentrated under reduced pressure and the crystallized product was collected by filtration and dried to give 2.13 g of the title compound, mp 136-139°.

Anal. Calcd for $C_{24}H_{45}N_5O_3S_2$: C, 55.89; H, 8.79; N, 13.58; S, 12.43.

Found: C, 56.16; H, 8.57; N, 13.38; S, 12.61.

Example 107

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-methoxyamino-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 13 was repeated,

except that the 2-propynylamine utilized therein was replaced by an equimolar amount of methoxyamine. The reaction mixture was stirred at ambient temperature overnight, during which a crystalline precipitate formed. The solution was cooled and filtered, and the recovered solid was dried to yield 3.8 g of the title compound, mp 224-226 (dec.).

Anal. Calcd for $C_{13}H_{21}N_5O_4S_2$: C, 41.59; H, 5.64; N, 18.65; S, 17.08.

Found (corr. for 0.79% $H_2O$): C, 41.25; H, 5.54; N, 18.50; S, 17.16.

## Example 108

3-{2-[(5-Dimethylaminomethyl-2-thienyl)methylthio]ethylamino}-4-propylamino-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 65 was repeated, except that the methylamine utilized therein was replaced by an equimolar amount of propylamine. Chromatography gave 3.5 g of crystalline product. Recrystallization from acetonitrile yielded the title compound, mp 194-196° (dec.).

Anal. Calcd for $C_{15}H_{25}N_5O_2S_3$: C, 44.64; H, 6.24; N, 17.35; S, 23.84.

Found: C, 44.66; H, 6.02; N, 17.88; S, 23.87.

## Example 109

3-Amino-4-{2-[(5-dimethylaminomethyl-2-thienyl)methylthio]-ethylamino}-1,2,5-thiadiazole 1-oxide

A solution of 2-[(5-dimethylaminomethyl-2-thienyl)-methylthio]ethylamine (2.84 g; 12.3 mmoles) in 25 ml of methanol was added dropwise over a period of 35 minutes to a stirred solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide

(2.0 g; 12.3 mmoles) in 200 ml of methanol that had been cooled to 3° in an ice-water bath. After stirring for 15 minutes, anhydrous ammonia was bubbled into the solution for 5 minutes. The reaction mixture was evaporated under reduced pressure, and the residue placed on 60 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined to give 1.73 g of product. Recrystallization from acetonitrile yielded the title compound, mp 149-152° (dec.).

## Example 110

### 3-{2-[(5-Dimethylaminomethyl-2-thienyl)methylthio]ethylamino}-4-[(3-pyridyl)methylamino]-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 65 was repeated, except that the methylamine utilized therein was replaced by an equimolar amount of 3-aminomethylpyridine. The appropriate fractions from column chromatography gave 3.10 g of the title compound as an oil. The product was dissolved in excess 5% HCl, evaporated and then triturated with isopropyl alcohol to give a solid product. Recrystallization from 95% aqueous ethanol yielded the title compound as a dihydrochloride salt, mp 143-146.5°.

Anal. Calcd for $C_{18}H_{26}Cl_2N_6O_2S_3$: C, 41.13; H, 4.99; N, 15.99; S, 18.30.

Found (corr. for 2.04% $H_2O$): C, 41.25; H, 4.90, N, 16.18; S, 18.52.

Example 111

3-Amino-4-{2-[(5-dimethylaminomethyl-2-thienyl)methylthio]-ethylamino}-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(5-dimethylaminomethyl-2-thienyl)-methylthio]ethylamine (2.0 g; 8.68 mmoles) in 25 ml of methanol was added dropwise over a period of 35 minutes to a stirred solution of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (1.55 g; 8.68 mmoles) in 200 ml of methanol that had been cooled to 3° in an ice-water bath. After stirring for 15 minutes, anhydrous ammonia was bubbled through the solution for 10 minutes. The reaction mixture was evaporated under reduced pressure to give 3.3 g of the title compound.

The NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide gave the following resonances δ: 6.88 (d, 1H); 6.78 (d, 1H); 4.03 (s, 2H); 3.61 (s, 2H); 3.54 (t, 2H); 2.74 (t, 2H); 2.22 (s, 6H); it also showed the presence of approximately 2/3 mole of methanol.

Example 112

3-Benzylamino-4-{2-[(5-dimethylaminomethyl-2-thienyl)-methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 65 was repeated, except that the methylamine utilized therein was replaced by an equimolar amount of benzylamine. The reaction mixture was evaporated under reduced pressure to give product. Recrystallization from methanol with charcoal treatment yielded 2.63 g of the title compound, mp 203-205.5° (dec.).

Anal. Calcd for $C_{19}H_{25}N_5O_2S_3$: C, 50.53; H, 5.58; N, 15.51; S, 21.30.
Found: C, 50.79; H, 5.34; N, 15.78; S, 20.94.

## Example 113

### 3-[3-(3-Dimethylaminomethylphenoxy)propylamino]-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A solution of 3-[3-(dimethylaminomethyl)phenoxy]-propylamine (2.73 g; 14.0 mmoles) [prepared according to the procedure described in Belgian Patent 867,106] in 50 ml of methanol was added dropwise over a period of 60 minutes to a stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.5 g; 14.0 mmoles) in 250 ml of methanol that had been cooled to 4° in an ice-water bath. After stirring for 20 minutes, anhydrous methylamine was bubbled into the solution for 10 minutes. The reaction mixture was evaporated under reduced pressure and the residue placed on 75 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined and evaporated, and then dissolved in n-propanol and treated with one equivalent of HCl to give the product as a hydrochloride salt. Recrystallization from aqueous ethanol yielded the title compound as a hydrochloride salt, mp 140-145°.

Anal. Calcd for $C_{15}H_{24}ClN_5O_3S$: C, 46.20; H, 6.20; N, 17.96; S, 8.22; Cl, 9.09.
Found (corr. for 3.79% $H_2O$): C, 46.21; H, 6.06, N, 18.24; S, 8.38; Cl, 9.05.

## Example 114

### 3-{2-[(2-Dimethylaminomethylthiazol-5-yl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A. 5-Carbethoxy-2-(N-carbophenoxy-N-methylamino)-methylthiazole

(N-Carbophenoxy-N-methylamino)thioacetamide (46.7 g; 0.21 moles) was combined with ethyl α-formylchloroacetate (30.0 g; 0.20 moles) in 270 ml of 1,2-dichloroethane and heated to reflux temperature for 2 hours. An additional amount of ethyl α-formylchloroacetate (3.0 g; 0.02 moles) was added and heating was continued for 1.5 hours. The reaction mixture was extracted with two 300 ml portions of cold 5% aqueous sodium carbonate, then washed with two 300 ml portions of water and dried over $Na_2SO_4$. Evaporation gave the product as an oil which slowly crystallized. Recrystallization from 2-propanol yielded 26 g of the title compound, mp 81-83°.

Anal. Calcd for $C_{15}H_{16}N_2O_4S$: C, 56.24; H, 5.03; N, 8.74; S, 10.01.

Found: C, 56.48; H, 4.97; N, 8.54; S, 10.17.

B. 2-Hydroxymethyl-5-dimethylaminomethylthiazole

5-Carbethoxy-2-(N-carbophenoxy-N-methylamino)-methylthiazole (19.8 g; 0.62 moles) [prepared in Step A] was added to a cold (5°) stirred suspension of lithium aluminum hydride (6.12 g; 0.16 moles) in 544 ml of dry tetrahydrofuran. The reaction mixture was heated to reflux temperature for 0.5 hour and then cooled to ambient temperature and decomposed, filtered through celite and evaporated

pressure and the residue made basic with 40% aqueous sodium hydroxide solution. The aqueous phase was extracted with methyl acetate and the organic phase was dried, filtered and evaporated to give 0.3 g of the title compound as an oil. The NMR spectrum (60 MHz) in $CDCl_3$ gave the following resonances δ: 7.50 (s, 1H), 3.95 (s, 2H); 3.76 (s, 2H); 2.85 (m, 4H); 2.40 (s, 6H), 1.85 (s, 2H).

E. 3-{2-[(2-Dimethylaminomethylthiazol-5-yl)-methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(2-dimethylaminomethylthiazol-5-yl)methylthio]ethylamine (1.55 g; 6.7 mmoles) [prepared in Step D] in 60 ml of methanol was added dropwise over 40 minutes to a partial suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (1.19 g; 6.7 mmoles) in 130 ml of methanol that had been cooled to 8°. Upon completion of the addition, anhydrous methylamine was bubbled into the solution for 8 minutes, then stirred at ambient temperature overnight. The reaction mixture was evaporated under reduced pressure and the residue chromatographed on 150 g of silica gel using a gradient elution of acetonitrile-methanol. The appropriate fractions were combined to give 1.05 g of product. Recrystallization from 2-propanol yielded the title compound, mp 170-172°.

Anal. Calcd for $C_{12}H_{20}N_6O_2S_3$: C, 38.28; H, 5.36; N, 22.33; S, 25.56.

Found: C, 38.31; H, 5.32; N, 22.13; S, 25.96.

Example 115

3-{2-[(2-Guanidinothiazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1-oxide

The general procedure of Example 31 is repeated except that the 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide utilized therein was replaced by an equimolar amount of the corresponding 1-oxide. The appropriate fractions from column chromatography were combined to give 4.5 g of product. Crystallization from absolute ethanol yielded 3.05 g of the title compound, mp 175-177°.

Anal. Calcd for $C_{10}H_{16}N_8OS_3$: C, 33.32; H, 4.47; N, 31.09; S, 26.68.

Found: C, 33.10; H, 4.42; N, 31.00; S, 26.51.

Example 116

3-{2-[(2-Guanidinothiazol-4-yl)methylthio]ethylamino}-4-hydroxy-1,2,5-thiadiazole 1-oxide

A solution of 2-[(2-guanidinothiazol-4-yl)methylthio]-ethylamine (4.15 g; 17.9 mmoles) in 50 ml of methanol was added dropwise over a 30 minute period to a solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (2.91 g; 17.9 mmoles) in 350 ml of methanol that had been cooled in an ice-water bath. The reaction mixture was treated with a solution of sodium hydroxide pellets (3.58 g; 89.5 mmoles) in methanol. After stirring overnight at ambient temperature, the mixture was neutralized with 14.9 ml (89.5 mmoles) of aqueous 6.0N HCl and after 10 minutes was evaporated under reduced pressure. The solid residue was triturated for 2 hours with 70 ml of water at ambient temperature and filtered to

give product. Recrystallization from water yielded the title compound, mp 148-151°.

Anal. Calcd for $C_9H_{13}N_7O_2S_3$: C, 31.11; H, 3.77; N, 28.22; S, 27.69.

Found (corr. for 5.52% $H_2O$): C, 30.95; H, 3.76; N, 28.27; S, 28.11.

## Example 117

### 3-Amino-4-{2-[(2-{2-methylguanidino}thiazol-4-yl)methylthio]-ethylamino}-1,2,5-thiadiazole 1-oxide

A. 2-{[2-(2-Methylguanidino)thiazol-4-yl]methylthio}-ethylamine

Cysteamine hydrochloride (1.89 g; 16.6 mmoles) and 2-(2-methylguanidino)-4-chloromethylthiazole hydrochloride (4.0 g; 16.6 mmoles) [prepared from (N-methylamidino)thiourea and 1,3-dichloro-2-propanone] were combined in 20 ml of concentrated hydrochloric acid and the solution was heated at an oil bath temperature of 100°. After 2 hours the mixture was evaporated under reduced pressure and the residue made basic with 40% aqueous NaOH solution. The aqueous phase was extracted several times with methyl acetate and the organic phase was dried, filtered and evaporated to give 3.35 g of the title compound. The NMR spectrum (60 MHz) in $D_2O$ gave the following characteristic resonances δ: 6.52 (s, 1H), 3.60 (s, 2H), 2.70 (m, 7H).

B. 3-Amino-4-{2-[(2-{2-methylguanidino}thiazol-4-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1-oxide

A solution of 2-[(2-{2-methylguanidino}thiazol-4-yl)methylthio]ethylamine (2.1 g; 8.56 mmoles) [prepared in

Step A] in 50 ml of methanol was added dropwise over 30 minutes to a solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (1.39 g; 8.56 mmoles) in 170 ml of methanol that had been cooled to 7°. Anhydrous ammonia was bubbled into the solution for 7 minutes, then stirred at ambient temperature overnight. The reaction mixture was evaporated under reduced pressure and the residue chromatographed on 100 g of silica gel (230-400 mesh) by flash chromatography using a gradient elution of acetonitrile-methanol. The appropriate fractions were combined, evaporated and the residue chromatographed on a Preparative HPLC system using μ-porasil silica gel. The appropriate fractions were combined, concentrated to a small volume and filtered to yield the title compound, mp 86-91°; the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the presence of approximately 0.8 moles of ethanol.

Anal. Calcd for $C_{10}H_{16}N_8OS_3 \cdot 0.8\ C_2H_6O$: C, 35.06; H, 5.28; N, 28.20; S, 24.21.

Found (corr. for 1.64% $H_2O$): C, 35.66; H, 5.05; N, 28.33; S, 23.96.

## Example 118

### 3-Amino-4-[3-(3-dimethylaminomethylphenoxy)propylamino]-1,2,5-thiadiazole 1-oxide

A solution of 3-[3-(dimethylaminomethyl)phenoxy]-propylamine (2.5 g; 12.9 mmoles) in 35 ml of methanol was added dropwise over a period of 30 minutes to a stirred solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide in 200 ml of methanol that had been cooled to 2° in an ice-water bath. After stirring for 15 minutes, anhydrous ammonia was bubbled into the solution for 5 minutes. The reaction mixture was evaporated under reduced pressure to give

crystalline product. Two recrystallizations from methanol yielded the title compound, mp 165.5-166.5° (dec.).

Anal. Calcd for $C_{14}H_{21}N_5O_2S$: C, 51.99; H, 6.55; N, 21.66; S, 9.92.

Found: C, 51.58; H, 6.49; N, 22.03; S, 10.19.

## Example 119

### 3-Amino-4-{2-[(2-methylaminothiazol-4-yl)methylthio]-ethylamino}-1,2,5-thiadiazole 1-oxide

A. 2-[(2-Methylaminothiazol-4-yl)methylthio]-ethylamine

Cysteamine hydrochloride (2.8 g; 24.6 mmoles) and 2-methylamino-4-chloromethylthiazole (4.0 g; 24.6 mmoles) [prepared from N-methylthiourea and 1,3-dichloro-2-propane] were dissolved in 20 ml of concentrated hydrochloric acid and the solution was heated at an oil bath temperature of 100°. After 30 hours of heating, the reaction mixture was evaporated under reduced pressure and the residue made basic with 40% aqueous NaOH solution. The aqueous phase was extracted with methyl acetate, dried, filtered and evaporated to give 1.75 g of the title compound as an oil which was used without further purification in Step B.

B. 3-Amino-4-{2-[(2-methylaminothiazol-4-yl)-methylthio]ethylamino}-1,2,5-thiadiazole 1-oxide

The product of Step A, above, was reacted sequentially with 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide and anhydrous ammonia according to the general procedure of Example 117, Step B, and chromatographed as described therein. The appropriate fractions from flash chromatography were combined and evaporated to give 0.5 g of product as a foam. Crystallization from acetone yielded the title compound, mp 180-183° (dec.).

Anal. Calcd for $C_9H_{14}N_6OS_3$ : C, 33.94; H, 4.43; N, 26.39; S, 30.21.

Found (corr. for 1.41% $H_2O$): C, 33.96; H, 4.11; N, 26.27; S, 30.44.

## Example 120

3-Amino-4-{2-[(2-{2,3-dimethylguanidino}thiazol-4-yl)-methylthio]ethylamino}-1,2,5-thiadiazole 1-oxide

A. 2-[(2-{2,3-Dimethylguanidino}thiazol-4-yl)-methylthio]ethylamine dihydrochloride

Cysteamine hydrochloride (2.25 g; 19.6 mmoles) and 4-chloromethyl-2-(2,3-dimethylguanidino)thiazole (5 g; 19.6 mmoles) [prepared from 1,3-dichloro-2-propanone and (N,N'-dimethylamidino)thiourea which is itself prepared from dimethyl cyanodithioiminocarbonate and methylamine] were dissolved in 17.5 ml of concentrated hydrochloric acid and heated at an oil bath temperature of 100°. After 24 hours the reaction mixture was evaporated under reduced pressure

and the residue crystallized from absolute ethanol to yield the title compound, mp 243-245°.

B. 3-Amino-4-{2-[(2-{2,3-dimethylguanidino}thiazol-4-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1-oxide

The product of Step A, above, was sequentially reacted with 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide and anhydrous ammonia by the general procedure of Example 117, Step B. The crude reaction mixture was evaporated under reduced pressure and the residue crystallized from methanol to give the title compound, mp 201-203° (dec.).

Anal. Calcd for $C_{11}H_{18}N_8OS_3$: C, 35.28; H, 4.84; N, 29.92; S, 25.69.

Found (corr. for 0.88% $H_2O$): C, 34.93; H, 4.56; N, 30.27; S, 25.92.

Example 121

3,4-Bis-{2-[(2-guanidinothiazol-4-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1-oxide

To a solution of sodium methoxide (2.16 g; 40.0 mmoles) in 100 ml of $CH_3OH$ that was cooled to 0° in an ice-water bath was added 2-[(2-guanidinothiazol-4-yl)methylthio]ethylamine dihydrochloride (6.09 g; 20.0 mmoles) and, after 20 minutes of stirring, the solution was treated with 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (1.62 g; 10 mmoles). The reaction mixture was stirred at ambient temperature for 65 hours and evaporated under reduced pressure. The residue was chromatographed

on 100 g of silica gel (230-400 mesh) by flash chromatography using a gradient elution of acetonitrile-methanol. The appropriate fractions were combined, evaporated and the residue chromatographed on a Preparative HPLC system using μ-porasil silica gel. The appropriate fractions were combined, and evaporated under reduced pressure to give the title compound as an amorphous solid; the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the presence of approximately 0.11 mole of ethanol.

Anal. Calcd for $C_{16}H_{24}N_{12}OS_5 \cdot 0.11C_2H_6O$: C, 34.42; H, 4.39; N, 29.71; S, 28.33.

Found (corr. for 1.86% $H_2O$): C, 34.95; H, 4.41; N, 29.04; S, 27.71.

## Example 122

### 3-{2-[(2-Aminothiazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A. 2-[(2-Aminothiazol-4-yl)methylthio]ethylamine dihydrochloride

Cysteamine hydrochloride (5.65 g; 50.0 mmoles) and 2-amino-4-chloromethylthiazole hydrochloride (9.25 g; 50.0 mmoles) were dissolved in 70 ml of concentrated hydrochloric acid and heated at an oil bath temperature of 105°. After 64 hours of heating the mixture was evaporated under reduced pressure and the residue triturated with acetone. The collected product was re-triturated with ethanol, filtered and dried to yield the title compound, mp 170-200°.

Anal. Calcd for $C_6H_{13}Cl_2N_3S_2$: C, 27.48; H, 4.90; N, 16.02; S, 24.46; Cl, 27.04.
Found: C, 27.29; H, 5.07; N, 15.91; S, 24.15; Cl, 27.24.

B. 3-{2-[(2-Aminothiazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(2-aminothiazol-4-yl)methylthio]-ethylamine (from the dihydrochloride, 3.0 g; 11.4 mmoles) [prepared in Step A] in 25 ml of methanol was added dropwise over 1.5 hours to a cold (5°), stirred, partial suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.03 g; 11.4 mmoles) in 55 ml of methanol. After 1.5 hours, anhydrous methylamine was bubbled into the solution for 30 minutes and stirred at 5° for 19 hours. The reaction mixture was evaporated under reduced pressure and the residue placed on 400 g of silica gel and chromatographed using acetone-methylene chloride (7:3). The appropriate fractions were combined and evaporated to give product. Recrystallization from 95% ethanol yielded the title compound, mp 200-201°.

Anal. Calcd for $C_9H_{14}N_6O_2S_3$: C, 32.32; H, 4.32; N, 25.13; S, 28.76.
Found: C, 32.25; H, 4.20; N, 25.06; S, 29.14.

Example 123

3-Amino-4-{2-[(2-dimethylaminomethylthiazol-5-yl)methylthio]-ethylamino}-1,2,5-thiadiazole 1-oxide

A solution of 2-[(2-dimethylaminomethylthiazol-5-yl)methylthio]ethylamine (2.05 g; 8.86 mmoles) [prepared in Example 114, Step D] in 70 ml of methanol was added dropwise to a cold (8°), stirred, solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (1.44 g; 8.88 mmoles) in 170 ml of methanol. Anhydrous ammonia was bubbled into the solution for 8 minutes and then stirred at ambient temperature for 0.5 hours. The reaction mixture was evaporated under reduced pressure and the residue triturated with acetonitrile to give 1.76 g of product. The product was purified by flash chromatography on 100 g of silica gel (230-400 mesh) using acetonitrile-methanol. The appropriate fractions were combined, evaporated and the residue crystallized from acetone to yield the title compound, mp 131-133°.

Anal. Calcd for $C_{11}H_{17}N_6OS_3$: C, 38.13; H, 5.24; N, 24.26; S, 27.76.

Found (corr. for 0.49% $H_2O$): C, 37.86; H, 5.06; N, 24.34; S, 27.68.

Example 124

3-Amino-4-{2-[(2-aminothiazol-4-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1-oxide

A solution of 2-[(2-aminothiazol-4-yl)methylthio]-ethylamine (from the dihydrochloride, 2.62 g; 10.0 mmoles)

[prepared in Example 122, Step A] in 20 ml of methanol was added dropwise over 30 minutes to a cold (5°) solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (1.62 g; 10.0 mmoles) in 50 ml of methanol. After stirring for 1.5 hours, anhydrous ammonia was bubbled into the solution for 30 minutes and the solution kept at 5° for 17 hours. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed on a Preparative HPLC system using μ-porasil silica gel. The appropriate fractions were combined and evaporated under reduced pressure to give the title compound as an amorphous solid; the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the presence of approximately 0.4 moles of ethanol.

Anal. Calcd for $C_8H_{12}N_6OS_3 \cdot 0.4C_2H_6O$: C, 32.74; H, 4.50; N, 26.03; S, 29.80.

Found (corr. for 1.39% $H_2O$): C, 32.39; H, 4.28; N, 28.39; S, 30.02.

## Example 125

### 3-Methylamino-4-{2-[(2-{2,3-dimethylguanidino}thiazol-4-yl)-methylthio]ethylamino}-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(2-{2,3-dimethylguanidino}thiazol-4-yl)methylthio]ethylamine (2.5 g; 9.64 mmoles) [prepared in Example 120, Step A] in methanol was added dropwise over a period of 40 minutes to a cold (8°), stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (1.72 g; 9.64 mmoles) in 270 ml of methanol. Anhydrous methylamine was bubbled into the solution for 7 minutes and the solution then was evaporated under reduced pressure. The residue was chromatographed on 100 g of silica gel (230-400 mesh) by flash chromatography and the appropriate fractions were combined and evaporated to give 2.5 g of product as a

foam. Crystallization from aqueous ethanol yielded the title compound, mp 132-137°.

Anal. Calcd for $C_{12}H_{20}N_8O_2S_3$: C, 35.63; H, 4.98; N, 27.70; S, 23.78.

Found (corr. for 4.78% $H_2O$): C, 35.74; H, 5.04; N, 27.87; S, 23.56.

## Example 126

### 3-{2-[(2-Dimethylaminothiazol-4-yl)methylthio]ethylamino}-4-amino-1,2,5-thiadiazole 1-oxide

A. 2-[(2-Dimethylaminothiazol-4-yl)methylthio]-ethylamine

Cysteamine hydrochloride (5.24 g; 45.9 mmoles) and 2-dimethylamino-4-chloromethylthiazole hydrochloride (9.8 g; 45.9 mmoles) [prepared from N,N-dimethylthiourea and 1,3-dichloro-2-propanone] were dissolved in 45 ml of concentrated hydrochloric acid and heated at an oil bath temperature of 100° for 96 hours. The mixture was evaporated under reduced pressure and the residue made basic with 40% aqueous NaOH. The aqueous phase was extracted with methyl acetate, dried and evaporated to give the title compound as an oil which was used without further purification in Step B.

The NMR spectrum (60 MHz) in $D_2O$ gave the following resonances δ: 6.97 (s, 1H); 3.94 (s, 2H); 3.67 (s, 3H); 3.15 (s, 3H); 3.05 (m, 4H).

B. 3-{2-[(2-Dimethylaminothiazol-4-yl)methylthio]-ethylamino}-4-amino-1,2,5-thiadiazole 1-oxide

A solution of 2-[(2-dimethylaminothiazol-4-yl)-

methylthio]ethylamine (3.5 g; 16.1 mmoles) [prepared in Step A] in 70 ml of methanol was added dropwise over a period of 30 minutes to a cold (7°), stirred solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (2.61 g; 16.1 mmoles) in 200 ml of methanol. Anhydrous ammonia was bubbled into the solution for 8 minutes and after stirring for 30 minutes the mixture was evaporated under reduced pressure. The residue was triturated with isopropyl alcohol then dissolved in methanol, filtered and evaporated to give product. The product was purified by flash chromatography on 100 g of silica gel (230-400 mesh) using methylene chloride-methanol. The appropriate fractions were combined and re-chromatographed by HPLC on a μ-porasil silica gel column. The appropriate fractions were combined and evaporated under reduced pressure to yield the title compound, mp 116-122°; the NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the presence of approximately 1/3 mole of ethanol.

Anal. Calcd for $C_{10}H_{16}N_6OS_3 \cdot 1/3\ C_2H_6O$: C, 36.83; H, 5.22; N, 24.16.

Found (corr. for 11.92% $H_2O$): C, 36.61; H, 4.06; N, 24.22.

## Example 127

### 3-{2-[(2-Dimethylaminothiazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(2-dimethylaminothiazol-4-yl)-methylthio]ethylamine (2.5 g; 11.5 mmoles) [prepared in Example 126, Step A] was added dropwise over a period of 30 minutes to a cold (7°), stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.05 g; 11.5 mmoles) in 200 ml of methanol. Anhydrous methylamine was bubbled

into the solution for 7 minutes and after stirring for 30 minutes, the mixture was evaporated under reduced pressure. The residue was crystallized from methanol to give 1.6 g of product. Two recrystallizations from 2-methoxyethanol yielded the title compound, mp 227-229°.

## Example 128

### 3-{2-[(2-{2-Imidazolidinyl}iminothiazol-4-yl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A. 2-[(2-{2-Imidazolidinyl}iminothiazol-4-yl)-methylthio]ethylamine

Cysteamine hydrochloride (2.22 g; 19.5 mmoles) and 2-[(2-imidazolidinyl)imino]-4-chloromethylthiazole hydrochloride (4.94 g; 19.51 mmoles) [prepared from 1,3-dichloro-2-propanone and N-(2-imidazolidin-2-yl)thiourea which is itself prepared from 2-(cyanimino)imidazolidine] were dissolved in 20 ml of concentrated hydrochloric acid and heated at an oil bath temperature of 100° for 5.5 hours. The reaction mixture was evaporated under reduced pressure and the residue made basic with 40% NaOH. The aqueous phase was extracted with methyl acetate, dried and evaporated to give 2.02 g of the title compound which was used in the next step without further purification.

B. 3-{2-[(2-{2-Imidazolidinyl}iminothiazol-4-yl)methylthio]ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(2-{2-imidazolidinyl}iminothiazol-4-yl)methylthio]ethylamine (2.02 g; 7.85 mmoles) [prepared in Step A] in 85 ml of methanol was added dropwise over 40

minutes to a cold (8°), stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (1.4 g; 7.85 mmoles) in 190 ml of methanol. Anhydrous methylamine was bubbled into the solution for 7 minutes and, after 30 minutes at ambient temperature, the mixture was evaporated under reduced pressure to give 3.5 g of product. The product was chromatographed on a Preparative HPLC system using μ-porasil silica gel. The appropriate fractions were combined, evaporated and the residue crystallized from methanol to give the title compound, mp 229-231°. Recrystallization from aqueous ethanol gave the title compound with mp 136-140° which resolidified with remelting at mp 219-224°.

Anal. Calcd for $C_{12}H_{18}N_8O_2S_3$: C, 35.81; H, 4.51; N, 27.84; S, 23.90.

Found (corr. for 4.59% $H_2O$): C, 35.51; H, 4.43; N, 27.98; S, 23.56.

## Example 129

### 3-{2-[(5-Dimethylaminomethyl-2-thienyl)methylthio]ethylamino}-4-[(2-pyridyl)methylamino]-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 65 was repeated except that the methylamine utilized therein was replaced by an equimolar amount of 2-aminomethylpyridine. Column chromatography of the crude solid yielded 3.08 g of product. Recrystallization from isopropyl alcohol yielded the title compound, mp 162-164° (dec.).

Anal. Calcd for $C_{18}H_{24}N_6O_2S_3$: C, 47.76; H, 5.34; N, 18.57.
Found: C, 47.80; H, 5.32; N. 18.75.

## Example 130

### 3-{2-[(5-Dimethylaminomethyl-2-thienyl)methylthio]ethylamino}-4-[(4-pyridyl)methylamino]-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 65 was repeated except that the methylamine utilized therein was replaced by an equimolar amount of 4-aminomethylpyridine. After chromatography the crude product was dissolved in hot isopropyl alcohol, decanted from insoluble material and the solution treated with anhydrous HCl to give the title compound as the hydrochloride salt. This salt was dissolved in water and made alkaline with saturated aqueous sodium bicarbonate solution to give, after filtration, the title compound as a free base, mp 88-90°.

Anal. Calcd for $C_{18}H_{24}N_6O_2S_3$: C, 47.76; H, 5.34; N, 18.57.
Found (corr. for 3.73% $H_2O$): C, 47.54; H, 5.32; N, 19.09.

## Example 131

### 3-{2-[(5-Dimethylaminomethyl-2-thienyl)methylthio]ethylamino}-4-ethylamino-1,2,5-thiadiazole 1,1-dioxide

The general procedure of Example 65 was repeated except that the methylamine utilized therein was replaced by an equimolar amount of ethylamine. The appropriate fractions from column chromatography were dissolved in warm isopropyl alcohol and saturated with anhydrous HCl. The crystalline solid was collected by filtration, washed with acetone and dried to give 2.9 g of the title compound as its hydrochloride salt, mp 246-247° (dec.).

Anal. Calcd for $C_{14}H_{24}ClN_5O_2S_3$: C, 39.47; H, 5.68; N, 16.44; Cl, 8.32.
Found: C, 39.81; H, 5.74; N, 16.62; Cl, 8.20.

## Example 132

### 3-Methylamino-4-[3-(3-piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1,1-dioxide

A solution of 3-(3-piperidinomethylphenoxy)propylamine (2.35 g; 9.45 mmoles) [prepared according to published U.K. patent application 2,023,133] in 30 ml of methanol was added dropwise over a period of 40 minutes to a stirred partial suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (1.68 g; 9.45 mmoles) that had been cooled to 1° in an ice-water bath. After 15 minutes, anhydrous methylamine was bubbled into the solution for 5 minutes and the solution then was stirred at ambient temperature for 30 minutes. The reaction mixture was evaporated under reduced pressure and the residue chromatographed by flash chromatography on 100 g of silica gel (230-400 mesh) using methanol-acetonitrile. The appropriate fractions were combined and evaporated to give 2.2 g of product. Recrystallization from acetonitrile with charcoal treatment yielded the title compound, mp 182-184°.

Anal. Calcd for $C_{18}H_{27}N_5O_3S$: C, 54.94; H, 6.92; N, 17.80; S, 8.15.
Found: C, 54.90; H, 7.07; N, 18.14; S, 8.29.

## Example 133

### 3-Amino-4-[3-(3-piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1-oxide

A solution of 3-(3-piperidinomethylphenoxy)propylamine (from the dihydrochloride, 4.0 g; 12.4 mmoles) in 40 ml of methanol was added dropwise over a period of 50 minutes to a solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (2.01 g; 12.4 mmoles) in 200 ml of methanol that had been cooled to 0° in an ice-water bath. After 15 minutes, anhydrous ammonia was bubbled into the solution for 5 minutes and the solution then was stirred at ambient temperature for 17 hours. The reaction mixture was evaporated under reduced pressure and the residue chromatographed by flash chromatography on 100 g of silica gel (230-400 mesh) using methanol-acetonitrile. The appropriate fractions were combined and evaporated to give 4.18 g of product. Recrystallization from 95% aqueous ethanol yielded the title compound, mp 155-157° (dec.).

Anal. Calcd for $C_{17}H_{25}N_5O_2S$: C, 56.17; H, 6.93; N, 19.27; S, 8.82.

Found: C, 55.97; H, 7.04; N, 19.57; S, 8.63.

## Example 134

### 3-Amino-4-[3-(3-piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1,1-dioxide

A solution of 3-(3-piperidinomethylphenoxy)-propylamine (from the dihydrochloride, 4.0 g; 12.4 mmoles) in 35 ml of methanol was added dropwise over a period of 65 minutes to a stirred partial suspension of 3,4-dimethoxy-

1,2,5-thiadiazole 1-oxide (2.22 g; 12.4 mmoles) in 200 ml of methanol that had been cooled to 2° in an ice-water bath. After 15 minutes anhydrous ammonia was bubbled into the solution for 5 minutes and the solution then was stirred at ambient temperature for 30 minutes. The reaction mixture was evaporated under reduced pressure and the residue placed on 100 g of silica gel (230-400 mesh) and chromatographed by flash chromatography using methanol-acetonitrile. The appropriate fractions were combined and evaporated to give 3.2 g of product. The NMR spectrum (100 MHz) in $d_6$ dimethyl sulfoxide showed the following resonances δ: 7.2 (m, 1H); 6.9 (m, 3H); 4.1 (t, 2H); 3.5 (t, 2H); 3.4 (s, 2H); 2.3 (m, 4H); 2.0 (m, 2H); 1.4 (broad s, 6H).

Example 135

3-{2-[(5-Dimethylaminomethyl-2-thienyl)methylthio]ethylamino}-4-(3,4-methylenedioxybenzylamino)-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(5-dimethylaminomethyl-2-thienyl)-methylthio]ethylamine (2.02 g; 8.8 mmoles) in 30 ml of methanol was added dropwise over a period of 40 minutes to a stirred solution of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (1.56 g; 8.8 mmoles) in 200 ml of methanol that had been cooled to 0° in an ice-water bath. After 20 minutes, piperonylamine (1.46 g; 9.6 mmoles) was added and the mixture stirred at ambient temperature for 3 hours. The reaction mixture was evaporated to near dryness, ether was added, and the mixture was filtered to give 3.47 g of product. Recrystallization from methanol yielded the title compound, mp 180-182°.

Anal. Calcd for $C_{20}H_{25}N_5O_4S_3$: C, 48.46; H, 5.08; N, 14.13.
Found (corr. for 0.38% $H_2O$): C, 48.92; H, 4.88; N. 14.52.

## Example 136

### 3-Amino-4-{2-[(6-dimethylaminomethyl-2-pyridyl)methylthio]-ethylamino}-1,2,5-thiadiazole 1-oxide

#### A. 6-(N,N-dimethylcarbamyl)-2-carbomethoxypyridine

A solution of 6-carbomethoxy-2-picolinic acid (22.8 g; 0.13 mole) in 80 ml of thionyl chloride was heated at an oil bath temperature of 100° for 3 hours. The solution was evaporated under reduced pressure and the residue dissolved in 200 ml of dioxane which then was added dropwise to a solution of dimethylamine (70 g) in dioxane. The reaction mixture was stirred for 2 hours and then allowed to stand at 4° overnight, filtered and evaporated under reduced pressure. The residue was dissolved in toluene, diluted with methylcyclohexane and filtered to give 20.7 g of the title compound, mp 90-92°.

Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46.
Found: C, 57.64; H, 5.85; N, 13.77.

#### B. 6-Dimethylaminomethyl-2-hydroxymethylpyridine

A solution of 6-(N,N-dimethylcarbamyl-2-carbomethoxypyridine (20.3 g; 97.5 mmoles) [prepared in Step A] in 200 ml of tetrahydrofuran was added to a suspension of lithium aluminum hydride (9.6 g; 0.25 moles) in 500 ml of tetrahydrofuran. The mixture was stirred and heated at reflux temperature under a nitrogen atmosphere for 3 hours then left at ambient temperature overnight. The mixture was decomposed with a saturated aqueous solution of $Na_2SO_4$,

filtered, dried and evaporated under reduced pressure. The residue was placed on 275 g of aluminum oxide and eluted with methylene chloride. The appropriate fractions were combined and evaporated to give 5.2 g of the title compound.

The NMR spectrum (60 MHz) in $CDCl_3$ gave the following resonances δ: 7.38 (m, 3H); 4.75 (s, 2H); 3.58 (s, 2H); 2.27 (s, 6H).

C. 2-[(6-Dimethylaminomethyl-2-pyridyl)methylthio]-ethylamine

Cysteamine hydrochloride (3.58 g; 31.5 mmoles) and 6-dimethylaminomethyl-2-hydroxymethylpyridine (5.0 g; 30.1 mmole) [prepared in Step B] were dissolved in 50 ml of 48% hydrobromic acid and the solution heated at reflux temperature for 12 hours and then allowed to stand at ambient temperature for 8 hours. The reaction mixture was evaporated under reduced pressure to half volume, made basic with 40% aqueous NaOH and extracted with several portions of methylene chloride. The combined organic phase was washed with a small amount of water and saturated brine solution then dried and evaporated under reduced pressure to yield 3.14 g of the title compound.

The NMR spectrum (60 MHz) in $CDCl_3$ gave the following resonances δ: 7.5 (m, 3H); 3.83 (s, 2H); 3.56 (s, 2H); 2.7 (m, 4H); 2.28 (s, 6H).

D. 3-Amino-4-{2-[(6-dimethylaminomethyl-2-pyridyl)-methylthio]ethylamino}-1,2,5-thiadiazole 1-oxide

When a methanolic solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide is successively treated with an equimolar

amount of 2-[(6-dimethylaminomethyl-2-pyridyl)methylthio]-ethylamine [prepared in Step C] and excess ammonia, the title compound is thereby produced.

Example 137

3-Amino-4-{2-[(6-dimethylaminomethyl-2-pyridyl)methylthio]-ethylamino}-1,2,5-thiadiazole 1,1-dioxide

When a methanolic solution of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is successively treated with an equimolar amount of 2-[(6-dimethylaminomethyl-2-pyridyl)-methylthio]ethylamine [prepared in Example 136, Step C] and excess ammonia, the title compound is thereby produced.

Example 138

3-{2-[(5-Guanidino-1,2,4-thiadiazol-3-yl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

When a methanolic solution of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is successively treated with an equimolar amount of 2-[(5-guanidino-1,2,4-thiadiazol-3-yl)-methylthio]ethylamine [prepared according to the procedure described in published European Patent Application 6679] and excess methylamine, the title compound is thereby produced.

Example 139

3-Amino-4-{2-[(5-guanidino-1,2,4-thiadiazol-3-yl)methylthio]-ethylamino}-1,2,5-thiadiazole 1,1-dioxide

When a methanolic solution of 3,4-dimethoxy-1,2,5-

thiadiazole 1,1-dioxide is successively treated with an equimolar amount of 2-[(5-guanidino-1,2,4-thiadiazol-3-yl)-methylthio]ethylamine and excess ammonia, the title compound is thereby produced.

Example 140

3-Amino-4-{2-[(5-guanidino-1,2,4-thiadiazol-3-yl)methylthio]-ethylamino}-1,2,5-thiadiazole 1-oxide

When a methanolic solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide is successively treated with an equimolar amount of 2-[(5-guanidino-1,2,4-thiadiazol-3-yl)-methylthio]ethylamine and excess ammonia, the title compound is thereby produced.

Example 141

3-{2-[(5-Guanidino-1,2,4-oxadiazol-3-yl)methylthio]-ethylamino}-4-methylamino-1,2,5-thiadiazole 1,1-dioxide

When a methanolic solution of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is successively treated with an equimolar amount of 2-[(5-guanidino-1,2,4-oxadiazol-3-yl)-methylthio]ethylamine [prepared according to the procedure described in published European Patent Application 6286] and excess methylamine, the title compound is thereby produced.

Example 142

3-Amino-4-{2-[(5-guanidino-1,2,4-oxadiazol-3-yl)methylthio]-ethylamino}-1,2,5-thiadiazole 1,1-dioxide

When a methanolic solution of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is successively treated with an equimolar amount of 2-[(5-guanidino-1,2,4-oxadiazol-3-yl)-methylthio]ethylamine and excess ammonia, the title compound is thereby produced.

## Example 143

3-Amino-4-{2-[(5-guanidino-1,2,4-oxadiazol-3-yl)methylthio]-ethylamino}-1,2,5-thiadiazole 1-oxide

When a methanolic solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide is successively treated with an equimolar amount of 2-[(5-guanidino-1,2,4-oxadiazol-3-yl)methylthio]-ethylamine and excess ammonia, the title compound is thereby produced.

## Example 144

The general procedure of Example 132 is repeated, except that the 3-(3-piperidinomethylphenoxy)propylamine utilized therein is replaced by an equimolar amount of

a) 3-(3-pyrrolidinomethylphenoxy)propylamine,
b) 3-[3-(4-methylpiperidino)methylphenoxy]propylamine,
c) 3-(3-homopiperidinomethylphenoxy)propylamine,
d) 3-(3-morpholinomethylphenoxy)propylamine[1] and
e) 3-[3-(N-methylpiperazino)methylphenoxy]propylamine[2], respectively,

and there is thereby produced

a) 3-Methylamino-4-[3-(3-pyrrolidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1,1-dioxide, mp 156-157°C,
b) 3-Methylamino-4-{3-[3-(4-methylpiperidino)methylphenoxy]-propylamino}-1,2,5-thiadiazole 1,1-dioxide, mp 186-189°C,

c) 3-Methylamino-4-[3-(3-homopiperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide, mp 174-176°C as the hydrochloride,
d) 3-Methylamino-4-[3-(3-morpholinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1,1-dioxide, mp 162-163°C, and
e) 3-Methylamino-4-{3-[3-(N-methylpiperazino)methylphenoxy]-propylamino}-1,2,5-thiadiazole 1,1-dioxide, respectively.

The above starting materials (1) and (2) are prepared by hydrogenation of a mixture of N-[3-(3-formylphenoxy)-propyl]phthalimide and the corresponding morpholine or N-methylpiperazine over 10% palladium/carbon catalyst and then removal of the phthalimido protecting group with hydrazine. The other starting materials are prepared according to the procedures described in published U.K. Patent Application 2,023,133.

Example 145

The general procedure of Example 133 is repeated, except that the 3-(3-piperidinomethylphenoxy)propylamine utilized therein is replaced by an equimolar amount of
a) 3-(3-pyrrolidinomethylphenoxy)propylamine,
b) 3-[3-(4-methylpiperidino)methylphenoxy]propylamine,
c) 3-(3-homopiperidinomethylphenoxy)propylamine,
d) 3-[3-(heptamethyleneiminomethyl)phenoxy]propylamine,
e) 3-(3-morpholinomethylphenoxy)propylamine and
f) 3-[3-(N-methylpiperazino)methylphenoxy]propylamine, respectively,
and there is thereby produced
a) 3-Amino-4-[3-(3-pyrrolidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1-oxide, mp 168-170°C (dec.)
b) 3-Amino-4-{3-[3-(4-methylpiperidino)methylphenoxy]-propylamino}-1,2,5-thiadiazole 1-oxide, mp 157-159°C,

c) 3-Amino-4-[3-(3-homopiperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1-oxide, mp 167-169°C,
d) 3-Amino-4-{3-[3-(heptamethyleneiminomethyl)phenoxy]-propylamino}-1,2,5-thiadiazole 1-oxide, mp 154-157°C,
e) 3-Amino-4-[3-(3-morpholinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1-oxide and
f) 3-Amino-4-{3-[3-(N-methylpiperazino)methylphenoxy]-propylamino}-1,2,5-thiadiazole 1-oxide, respectively.

Example 146

The general procedure of Example 134 is repeated, except that the 3-(3-piperidinomethylphenoxy)propylamine utilized therein is replaced by an equimolar amount of
a) 3-(3-pyrrolidinomethylphenoxy)propylamine,
b) 3-[3-(4-methylpiperidino)methylphenoxy]propylamine,
c) 3-(3-homopiperidinomethylphenoxy)propylamine,
d) 3-(3-morpholinomethylphenoxy)propylamine and
e) 3-[3-(N-methylpiperazino)methylphenoxy]propylamine,
respectively,
and there is thereby produced
a) 3-Amino-4-[3-(3-pyrrolidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1,1-dioxide, mp 160-163°C (dec.)
b) 3-Amino-4-{3-[3-(4-methylpiperidino)methylphenoxy]propylamino}-1,2,5-thiadiazole 1,1-dioxide,
c) 3-Amino-4-[3-(3-homopiperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1,1-dioxide,
d) 3-Amino-4-[3-(3-morpholinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1,1-dioxide, mp 172-174°C (dec.), and
e) 3-Amino-4-{3-[3-(N-methylpiperazino)methylphenoxy]-propylamino}-1,2,5-thiadiazole 1,1-dioxide, respectively.

Example 147

The general procedure of Example 132 is repeated, except that the methylamine utilized therein is replaced by an equimolar amount of
ethylamine,

propylamine,
n-butylamine,
allylamine,
2-propynylamine,
cyclopropylamine,
aminomethylcyclopropane,
ethanolamine,
2-methoxyethylamine,
2,2,2-trifluoroethylamine,
2-fluoroethylamine,
hydroxyamine,
3-aminopropionitrile
benzylamine,
3-methoxybenzylamine,
4-methoxybenzylamine,
3,4-dimethoxybenzylamine,
piperonylamine,
4-chlorobenzylamine,
2-aminomethylpyridine,
3-aminomethylpyridine and
4-aminomethylpyridine, respectively,
and there is thereby produced
3-Ethylamino-4-[3-(3-piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-Propylamino-4-[3-(3-piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-Butylamino-4-[3-(3-piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-Allylamino-4-[3-(3-piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-(2-Propynyl)amino-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-(Cyclopropylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,

3-[(Cyclopropyl)methylamino]-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-(2-Hydroxyethylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-(2-Methoxyethylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-(2,2,2-trifluoroethylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-(2-Fluoroethylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-Hydroxyamino-4-[3-(3-piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-(3-Cyanopropylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-Benzylamino-4-[3-(3-piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-(3-Methoxybenzylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-(4-Methoxybenzylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-(3,4-Dimethoxybenzylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-(3,4-Methylenedioxybenzylamino)-4-[3-(3-piperidinomethyl-phenoxy)propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-(4-Chlorobenzylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-[(2-Pyridyl)methylamino]-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide,
3-[(3-Pyridyl)methylamino]-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide, and
3-[(4-Pyridyl)methylamino]-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1,1-dioxide, respectively.

Example 148

The general procedures of Example 147 are repeated except that the 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide utilized therein is replaced by an equimolar amount of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide, and there are thereby produced

3-Ethylamino-4-[3-(3-piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1-oxide,

3-Propylamino-4-[3-(3-piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1-oxide,

3-Butylamino-4-[3-(3-piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1-oxide,

3-Allylamino-4-[3-(3-piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1-oxide,

3-(2-Propynyl)amino-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide,

3-(Cyclopropylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide,

3-[(Cyclopropyl)methylamino]-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide,

3-(2-Hydroxyethylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide,

3-(2-Methoxyethylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide,

3-(2,2,2-Trifluoroethylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide,

3-(2-Fluoroethylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide,

3-Hydroxyamino-4-[3-(3-piperidinomethylphenoxy)propylamino]-1,2,5-thiadiazole 1-oxide,

3-(3-Cyanopropylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide,

3-Benzylamino-4-[3-(3-piperidinomethylphenoxy)propylamino]-

1,2,5-thiadiazole 1-oxide,
3-(3-Methoxybenzylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide,
3-(4-Methoxybenzylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide,
3-(3,4-Dimethoxybenzylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide,
3-(3,4-Methylenedioxybenzylamino)-4-[3-(3-piperidinomethyl-phenoxy)propylamino]-1,2,5-thiadiazole 1-oxide,
3-(4-Chlorobenzylamino)-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide,
3-[(2-Pyridyl)methylamino]-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide
3-[(3-Pyridyl)methylamino]-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide, mp 139.5-143°C, and
3-[(4-Pyridyl)methylamino]-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide, respectively.

## Example 149

### 3-[(3-Pyridyl)methylamino]-4-[3-(3-piperidinomethylphenoxy)-propylamino]-1,2,5-thiadiazole 1-oxide

A solution of 3-(3-piperidinomethylphenoxy)propylamine (from the dihydrochloride, 3.21 g; 10.0 mmoles) in 30 ml of methanol was added dropwise over a period of 60 minutes to a partial solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (1.62 g; 10.0 mmoles) that had been cooled to 5-7° in an ice-water bath. After 3 hours at ambient temperature, a solution of 3-aminomethylpyridine (1.14 g; 10.5 mmoles) in 10 ml of methanol was added and the solution was then stirred for 18 hours. The reaction mixture was evaporated under reduced pressure and the residue chromatographed by flash

chromatography on 100 g of silica gel (230-400 mesh) using methylene chloride-methanol-ammonia. The appropriate fractions were combined, evaporated and triturated with acetonitrile to give 4.05 g of product. Recrystallization from isopropyl alcohol yielded the title compound, mp 139.5-143°.

Anal. Calc'd. for $C_{23}H_{30}N_6O_2S$: C, 60.77; H, 6.65; N, 18.49; S, 7.04.
Found: C, 60.66; H, 6.64; N, 18.22; S, 7.02.

## Example 150

### 3-Amino-4-[3-(3-guanidinophenoxy)propylamino]-1,2,5-thiadiazole 1-oxide

#### A. N-[3-(3-Nitrophenoxy)propyl]phthalimide

A partial suspension of m-nitrophenol (6.0 g; 43.0 mmoles), N-(3-bromopropyl)phthalimide (10.0 g; 37.0 mmoles) and potassium carbonate (8.0 g; 58.0 mmoles) in 50 ml of DMF was stirred at ambient temperature for 70 hours. The reaction mixture was diluted with 80 ml of water and filtered to give product. Recrystallization from 2-methoxyethanol yielded 9.15 g of the title compound, mp 149-152°.

Anal. Calc'd. for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59.
Found: C, 62.49; H, 4.30; N, 8.71.

#### B. N-[3-(3-Aminophenoxy)propyl]phthalimide

A suspension of N-[3-(3-nitrophenoxy)propyl]phthalimide (1.0 g; 3.1 mmoles) [prepared in Step A] and 10% palladium on carbon (0.2 g) in 100 ml of 2-methoxyethanol was hydrogenated in a Parr Apparatus at ambient temperature for 45 minutes. The reaction mixture was filtered and the filtrate was evaporated to dryness to give 0.91 g of crude product.

An analytical sample was prepared by flash chromatography on silica gel using methylene chloride-methanol and recrystallization from absolute ethanol yielded the title compound, mp 157-162°.

Anal. Calc'd. for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45.
Found: C, 69.00; H, 5.54; N, 9.52.

C. N-[3-(3-Guanidinophenoxy)propyl]phthalimide

A mixture of crude N-[3-(3-aminophenoxy)propyl]-phthalimide (13.27 g; 45.0 mmoles) [prepared in Step B], 50% aqueous cyanamide (7.9 ml) and 12N hydrochloric acid (3.78 ml; 45.0 mmoles) in 39.4 ml of absolute ethanol was heated at reflux for 2-1/4 hours. An additional 7.9 ml of 50% aqueous cyanamide was added and heating was continued for 15 hours. The reaction mixture was evaporated under reduced pressure and the residue chromatographed by flash chromatography on 120 g of silica gel (230-400 mesh) using methylene chloride-methanol. The appropriate fractions were combined, evaporated and triturated with cold acetonitrile to give 5.85 g of product. Recrystallization from absolute ethanol yielded the title compound as a hydrochloride salt, mp 185-187°.

Anal. Calc'd. for $C_{18}H_{18}N_4O_3 \cdot HCl$: C, 57.68; H, 5.11; N. 14.95; Cl, 9.46.
Found: C, 57.65; H, 5.55; N, 15.08; Cl, 9.16.

D. 3-(3-Guanidinophenoxy)propylamine

To a partial suspension of N-[3-(3-guanidinophenoxy)-propyl]phthalimide hydrochloride (1.0 g; 2.95 mmoles) in 10 ml of 95% aqueous ethanol was added 0.27 ml of hydrazine hydrate. The mixture was stirred at ambient temperature for 17 hours and evaporated under reduced pressure to give the title compound. The product was used without further purification in Step E.

E. 3-Amino-4-[3-(3-guanidinophenoxy)propylamino]-1,2,5-thiadiazole 1-oxide

To a solution of crude 3-(3-guanidinophenoxy)propylamine [prepared in Step D] in 10 ml of methanol was added 3-amino-4-methoxy-1,2,5-thiadiazole 1-oxide (0.59 g; 4.0 mmoles) and the mixture was stirred at ambient temperature for 17 hours and then heated at 50° for 2.5 hours. The reaction mixture was filtered, evaporated under reduced pressure and the residue was chromatographed by flash chromatography on 75 g of silica gel (230-400 mesh) using methanol-methylene chloride. The appropriate fractions were combined and evaporated under reduced pressure to yield 0.25 g of the title compound as an oil; TLC [silica gel/$CH_2Cl_2$:$CH_3OH$ (4:1)] gave Rf=0.21.

The NMR spectrum (60 MHz) in $d_6$ dimethyl sulfoxide gave the following resonances δ: 9.33 (s, 1H); 8.43 (s, 2H); 7.52 (m, 4H); 7.43 (m, 1H); 6.83 (m, 3H); 4.13 (broad t, 2H); 3.51 (broad t, 2H); 2.10 (broad t, 2H).

## Example 151

3-Amino-4-{2-[(5-piperidinomethyl-2-furyl)methylthio]-ethylamino}-1,2,5-thiadiazole 1-oxide

A. 3-Amino-4-methoxy-1,2,5-thiadiazole 1-oxide

A 2.75 N solution of ammonia (56.0 ml; 0.154 mmole) in methanol was added dropwise over 1 hour to a well-stirred solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (24.3 g; 0.15 mole) in 725 ml of methanol at 20°. The resultant solution was stirred at ambient temperature for 3 hours and then was concentrated to about 125 ml at reduced pressure. After 16 hours at 0°, the mixture was filtered and dried to give 19.9 g of product.

An analytical sample was prepared by recrystallization from methanol to yield the title compound, mp 182-184° (dec.)

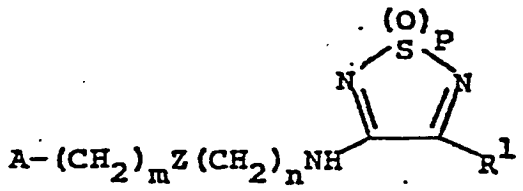
Anal. Calc'd. for $C_3H_5N_3O_2S$: C, 24.49; H, 3.43; N, 28.56; S, 21.79.
Found: C, 24.22; H, 3.63; N, 28.60; S, 21.92.

B. 3-Amino-4-{2-[(5-piperidinomethyl-2-furyl)-methylthio]ethylamino}-1,2,5-thiadiazole 1-oxide

A solution of 2-[(5-piperidinomethyl-2-furyl)methylthio]-ethylamine (4.0 g; 15.7 mmoles) [prepared according to the procedure described in Belgian Patent 857,388 (U.S. Patent 4,128,658)] in 25 ml of methanol was added all at once to a stirred suspension of 3-amino-4-methoxy-1,2,5-thiadiazole 1-oxide (2.31 g; 15.7 mmoles) [prepared in Step A] in 25 ml of methanol at ambient temperature. After stirring for 16 hours, the solution was evaporated under reduced pressure and the residue chromatographed by flash chromatography on 100 g of silica gel (230-400 mesh) using methanol-acetonitrile. The appropriate fractions were combined and evaporated to give 3.71 g of product. Recrystallization from 95% aqueous ethanol with charcoal treatment yielded the title compound, mp 161-163°.
Anal. Calc'd. for $C_{15}H_{23}N_5O_2S_2$: C, 48.76; H, 6.27; N, 18.96; S, 17.36.
Found: C, 48.86; H, 6.16; N, 19.66; S, 17.63.

C l a i m s

1. A pharmaceutical composition useful in the treatment of peptic ulcers, which comprises a peptic activity-inhibiting amount of pepstatin and an effective anti-ulcerogenic amount of at least one compound of the formula I:



(I)

wherein p is 1 or 2;

$R^1$ is hydroxy or $NR^2R^3$;

$R^2$ and $R^3$ each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxy(lower)alkyl, (lower)-alkylthio(lower)alkyl, 2-fluoroethyl, 2,2,2-trifluoroethyl or cyano(lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ may also be cyclo(lower)alkyl, amino(lower)alkyl, (lower)alkylamino(lower)-alkyl, di(lower)alkylamino(lower)alkyl, pyrrolidino(lower)alkyl, piperidino(lower)alkyl, morpholino(lower)alkyl, piperazino(lower)-alkyl, pyridyl(lower)alkyl, substituted pyridyl(lower)alkyl wherein the pyridyl ring may contain one substituent selected from (lower)alkyl, (lower)alkoxy, hydroxy, amino and halogen, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, (lower)-alkoxy, 2,3-dihydroxypropyl, cyano, amidino, (lower)alkylamidino, $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$, phenyl, phenyl(lower)alkyl, substituted phenyl or substituted phenyl(lower)alkyl, wherein the phenyl ring

may contain one or two substituents independently selected from (lower)alkyl, hydroxy, (lower)alkoxy and halogen or one substituent selected from methylenedioxy, trifluoromethyl and di(lower)alkylamino; or $R^2$ and $R^3$, taken together, may be $-CH_2CH_2X(CH_2)_r-$;

r is an integer of from 1 to 3, inclusive;

X is methylene, sulfur, oxygen or $N-R^4$, provided that, when r is 1, X is methylene;

$R^4$ is hydrogen, (lower)alkyl, (lower)alkenyl, (lower)-alkynyl, (lower)alkanoyl or benzoyl;

m and m' each are independently an integer of from zero to 2, inclusive;

n and n' each are independently an integer of from 2 to 4, inclusive;

Z and Z' each are independently sulfur, oxygen or methylene;

A and A' each are independently phenyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, furyl, thienyl or pyridyl; provided that A and A' independently may contain one or two substituents, the first substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl, (lower)alkoxy,

$$-(CH_2)_qN=C\begin{matrix}\diagup NHR^{14}\\ \diagdown NHR^{15}\end{matrix} \quad \text{and} \quad -(CH_2)_qNR^5R^6,$$

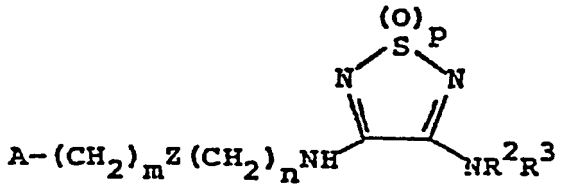
and the second substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl and (lower)alkoxy;

q is an integer of from 0 to 6, inclusive; $R^{14}$ and $R^{15}$ independently are hydrogen or (lower)alkyl, or, if $R^{14}$ is hydrogen, $R^{15}$ also may be (lower)alkanoyl or benzoyl, or $R^{14}$ and $R^{15}$, taken together, may be ethylene; and

$R^5$ and $R^6$ each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkoxy(lower)alkyl, cyclo(lower)alkyl, phenyl or phenyl(lower)alkyl, provided that $R^5$ and $R^6$ may not both be cyclo(lower)alkyl or phenyl; or $R^5$ and

$R^6$, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, dimethylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, dimethylpiperidino, hydroxypiperidino, N-methylpiperazino, homopiperidino, heptamethyleneimino or octamethyleneimino, or a nontoxic, pharmaceutically acceptable salt, hydrate or solvate thereof.

2. A composition of Claim 1 wherein the compound of Formula I has the structure



wherein p is 1 or 2;

$R^2$ and $R^3$ each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxy(lower)alkyl, (lower)-alkylthio(lower)alkyl, 2-fluoroethyl, 2,2,2-trifluoroethyl or cyano(lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ may also be cyclo(lower)alkyl, amino(lower)alkyl, (lower)alkylamino(lower)-alkyl, di(lower)alkylamino(lower)alkyl, pyrrolidino(lower)alkyl, piperidino(lower)alkyl, morpholino(lower)alkyl, piperazino(lower)-alkyl, pyridyl(lower)alkyl, substituted pyridyl(lower)alkyl wherein the pyridyl ring may contain one substituent selected from (lower)alkyl, (lower)alkoxy, hydroxy, amino and halogen, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, (lower)-alkoxy, 2,3-dihydroxypropyl, cyano, amidino, (lower)alkylamidino, $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$, phenyl, phenyl(lower)alkyl, substituted phenyl or substituted phenyl(lower)alkyl, wherein the phenyl ring may contain one or two substituents independently selected from (lower)alkyl, hydroxy, (lower)alkoxy and halogen or one substituent selected from methylenedioxy, trifluoromethyl and di(lower)alkylamino; or $R^2$ and $R^3$, taken together, may be $-CH_2CH_2X(CH_2)_r-$;

r is an integer of from 1 to 3, inclusive;

X is methylene, sulfur, oxygen or N-$R^4$, provided that, when r is 1, X is methylene;

$R^4$ is hydrogen, (lower)alkyl, (lower)alkenyl, (lower)-alkynyl, (lower)alkanoyl or benzoyl;

m and m' each are independently an integer of from zero to 2, inclusive;

n and n' each are independently an integer of from 2 to 4, inclusive;

Z and Z' each are independently sulfur, oxygen or methylene;

A and A' each are independently phenyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, furyl, thienyl or pyridyl; provided that A and A' independently may contain one or two substituents, the first substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl, (lower)alkoxy,

$$-(CH_2)_q N=C\begin{matrix}NHR^{14}\\ \diagdown\\ \diagup\\ NHR^{15}\end{matrix}$$ and $$-(CH_2)_q NR^5R^6,$$

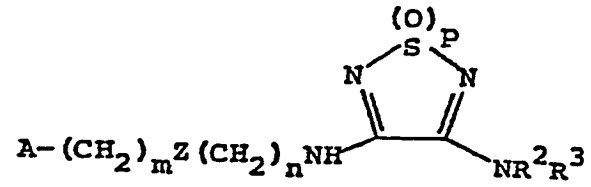
and the second substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl and (lower)alkoxy;

q is an integer of from 0 to 6, inclusive; $R^{14}$ and $R^{15}$ independently are hydrogen or (lower)alkyl, or, if $R^{14}$ is hydrogen, $R^{15}$ also may be (lower)alkanoyl or benzoyl, or $R^{14}$ and $R^{15}$, taken together, may be ethylene; and

$R^5$ and $R^6$ each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkoxy(lower)alkyl, cyclo(lower)alkyl, phenyl or phenyl(lower)alkyl, provided that $R^5$ and $R^6$ may not both be cyclo(lower)alkyl or phenyl; or $R^5$ and $R^6$, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, dimethyl-pyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, dimethylpiperidino, hydroxypiperidino, N-methylpiperazino, homopiperidino, heptamethyleneimino or

octamethyleneimino, or a nontoxic, pharmaceutically acceptable salt, hydrate or solvate thereof.

3. A composition of Claim 1 wherein the compound of Formula I has the structure



wherein p is 1 or 2;

$R^2$ and $R^3$ each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxy(lower)alkyl, 2-fluoroethyl or 2,2,2-trifluoroethyl, or, when $R^2$ is hydrogen, $R^3$ also may be pyrrolidino(lower)alkyl, piperidino(lower)alkyl, morpholino-(lower)alkyl, piperazino(lower)alkyl, pyridyl(lower)alkyl, substituted pyridyl(lower)alkyl wherein the pyridyl ring may contain one substituent selected from (lower)alkyl, (lower)-alkoxy, hydroxy, amino and halogen, hydroxy, $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$, phenyl(lower)alkyl or substituted phenyl(lower)alkyl, wherein the phenyl ring may contain one or two substituents independently selected from (lower)alkyl, hydroxy, (lower)alkoxy and halogen or one substituent selected from methylenedioxy, trifluoromethyl and di(lower)alkylamino;

m and m' each are independently an integer of from zero to 2, inclusive;

n and n' each are independently an integer of from 2 to 4, inclusive;

Z and Z' each are independently sulfur, oxygen or methylene;

A and A' each are independently phenyl, imidazolyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, furyl, thienyl or pyridyl; provided that A and A' independently may contain one or two substituents, the first substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl, (lower)alkoxy,

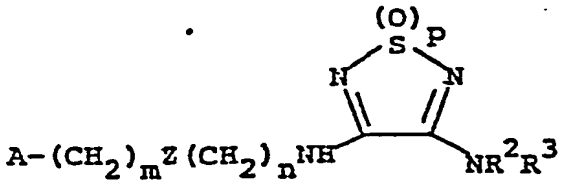
$-(CH_2)_qN=C(NHR^{14})(NHR^{15})$ and $-(CH_2)_qNR^5R^6$,

and the second substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl and (lower)alkoxy;

q is an integer of from 0 to 6, inclusive; $R^{14}$ and $R^{15}$ independently are hydrogen or (lower)alkyl, or $R^{14}$ and $R^{15}$, taken together, may be ethylene; and

$R^5$ and $R^6$ each are independently hydrogen, (lower)alkyl, (lower)alkenyl or (lower)alkynyl; or $R^5$ and $R^6$, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, dimethylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, dimethylpiperidino, hydroxypiperidino, N-methylpiperazino, homopiperidino, heptamethyleneimino or octamethyleneimino, or a nontoxic pharmaceutically acceptable salt, hydrate or solvate thereof.

4. A composition of Claim 1 wherein the compound of Formula I has the structure




wherein p is 1 or 2;

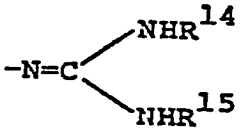
$R^2$ and $R^3$ each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl or cyclo(lower)alkyl(lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ also may be pyridyl(lower)alkyl, substituted pyridyl(lower)alkyl wherein the pyridyl ring may contain one substituent selected from (lower)alkyl, (lower)alkoxy, hydroxy, amino and halogen, $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$, phenyl(lower)-alkyl or 3,4-methylenedioxybenzyl;

m and m' each are independently zero or 1;

n and n' each are independently 2 or 3;

Z and Z' each are independently sulfur, oxygen or methylene;

A and A' each are independently phenyl, imidazolyl, thiazolyl, furyl, thienyl or pyridyl; provided that A and A' independently may contain one or two substituents, the first substituent being selected from (lower)alkyl,



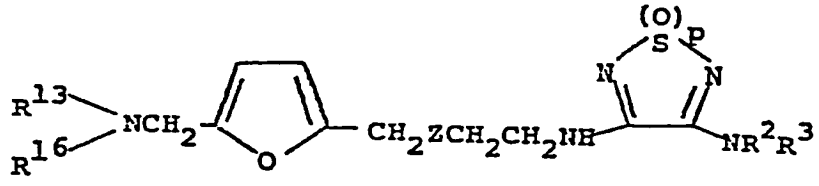
and $-CH_2NR^5R^6$,

and the second substituent being selected from (lower)alkyl;

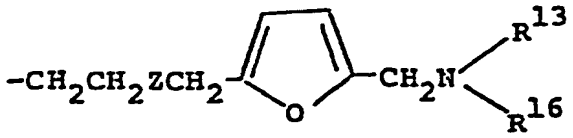
$R^{14}$ and $R^{15}$ independently are hydrogen or (lower)alkyl, or $R^{14}$ and $R^{15}$, taken together, may be ethylene; and

$R^5$ and $R^6$ each are independently hydrogen or (lower)-alkyl; or $R^5$ and $R^6$, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, dimethylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, dimethylpiperidino, hydroxypiperidino, N-methylpiperazino, homopiperidino, heptamethyleneimino or octamethyleneimino, or a nontoxic, pharmaceutically acceptable salt, hydrate or solvate thereof.

5. A composition of Claim 1 wherein the compound of Formula I has the structure



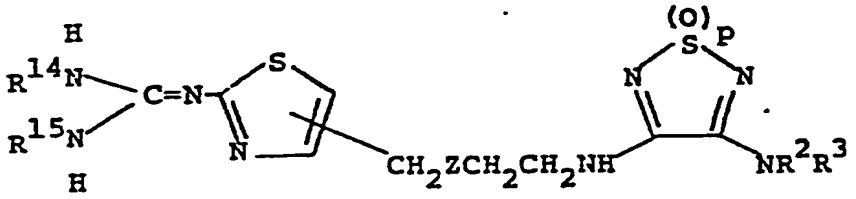
wherein p is 1 or 2; Z is sulfur or methylene; $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ also may be (lower)alkenyl, (lower)alkynyl, phenyl(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, pyridylmethyl or



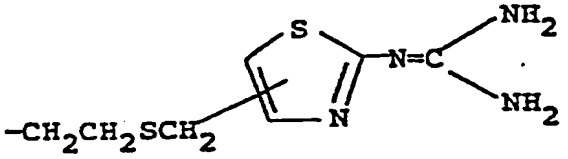
;

$R^{16}$ is methyl and $R^{13}$ is hydrogen or methyl, or $R^{16}$ and $R^{13}$, taken together with the nitrogen atom to which they are attached, may be piperidino; or a nontoxic pharmaceutically acceptable salt, hydrate or solvate thereof.

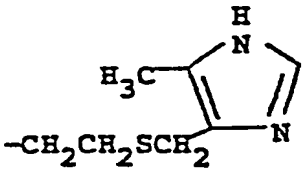
6. A composition of Claim 1 wherein the compound of Formula I has the structure



wherein p is 1 or 2; Z is sulfur or methylene; $R^{14}$ and $R^{15}$ independently are hydrogen or methyl, or, $R^{14}$ and $R^{15}$, taken together, may be ethylene; and $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ also may be (lower)alkenyl, (lower)alkynyl, pyridylmethyl,



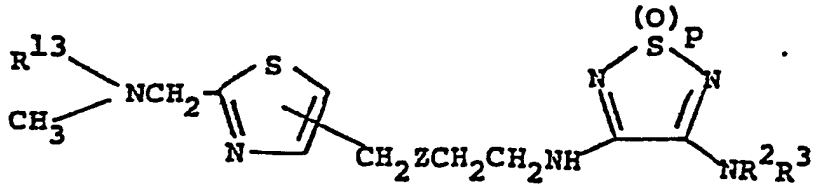
or



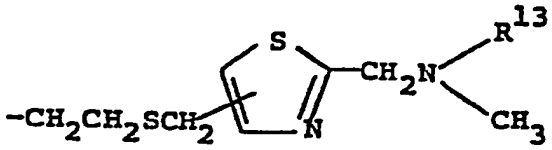
;

or a nontoxic, pharmaceutically acceptable salt, hydrate or solvate thereof.

7. A composition of Claim 1 wherein the compound of Formula I has the structure



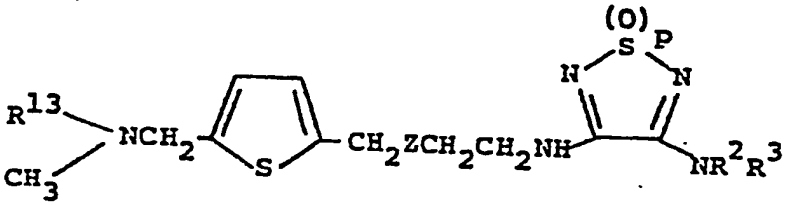
wherein p is 1 or 2; Z is sulfur or methylene; $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or when $R^2$ is hydrogen, $R^3$ also may be (lower)alkenyl, (lower)alkynyl or



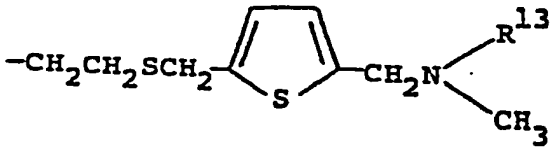
;

and $R^{13}$ is hydrogen or methyl; or a nontoxic pharmaceutically acceptable salt, hydrate or solvate thereof.

8. A composition of Claim 1 wherein the compound of Formula I has the structure



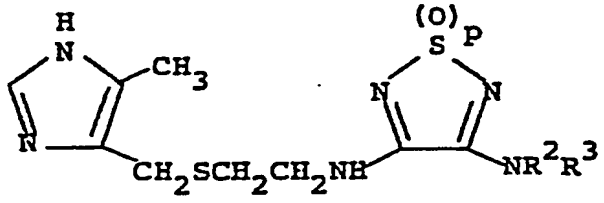
wherein p is 1 or 2; Z is sulfur or methylene; $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ also may be (lower)alkenyl, (lower)alkynyl, phenyl(lower)alkyl, pyridylmethyl, 3,4-methylenedioxybenzyl or



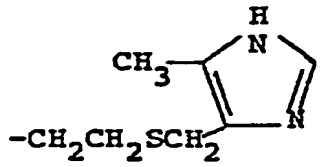
;

and $R^{13}$ is hydrogen or methyl; or a nontoxic pharmaceutically acceptable salt, hydrate or solvate thereof.

9. A composition of Claim 1 wherein the compound of Formula I has the structure



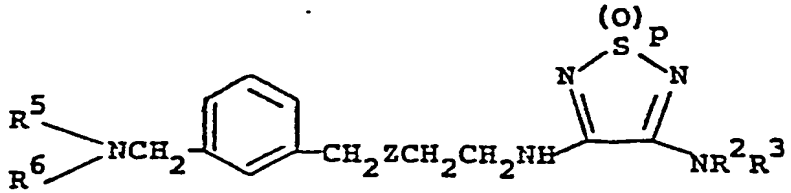
wherein p is 1 or 2; and $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ also may be (lower)alkenyl, (lower)alkynyl or



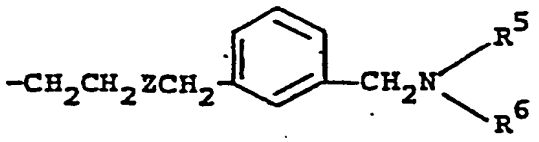
;

or a nontoxic, pharmaceutically acceptable salt, hydrate or solvate thereof.

10. A composition of Claim 1. wherein the compound of Formula I has the structure



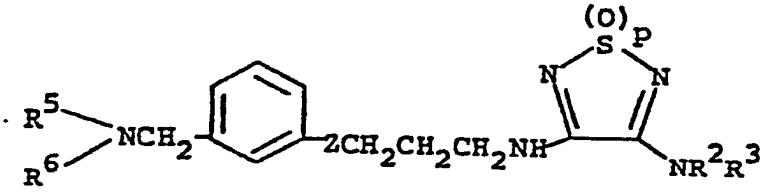
wherein p is 1 or 2; Z is sulfur or methylene; $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ also may be (lower)alkenyl, (lower)alkynyl or



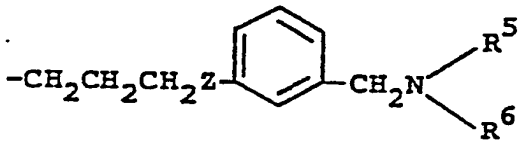
;

and $R^5$ and $R^6$ each are independently hydrogen or (lower)alkyl, or, $R^5$ and $R^6$, taken together with the nitrogen atom to which they are attached, may be piperidino; or a nontoxic, pharmaceutically acceptable salt, hydrate or solvate thereof.

11. A composition of Claim 1 wherein the compound of Formula I has the structure



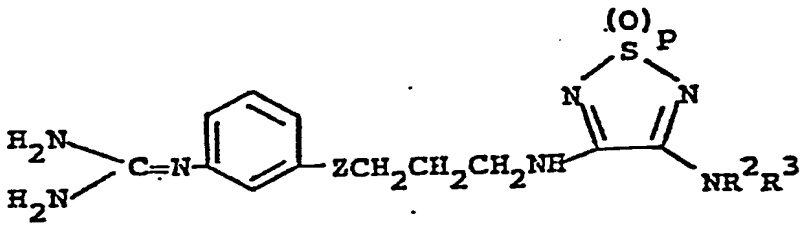
wherein p is 1 or 2; Z is oxygen or sulfur; $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ also may be (lower)alkenyl, (lower)alkynyl, pyridylmethyl or



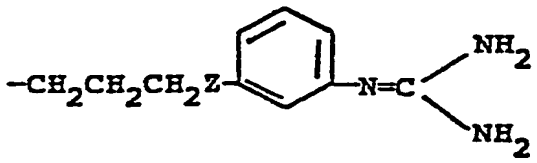
;

and $R^5$ and $R^6$ each are independently hydrogen or (lower)alkyl, or, when $R^5$ is hydrogen, $R^6$ also may be (lower)alkenyl or (lower)alkynyl; or $R^5$ and $R^6$, taken together with the nitrogen to which they are attached, may be pyrrolidino, methylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, dimethylpiperidino, homopiperidino or heptamethyleneimino; or a nontoxic, pharmaceutically acceptable salt, hydrate or solvate thereof.

12. A composition of claim 1 wherein the compound of formula I has the structure



wherein p is 1 or 2; Z is oxygen or sulfur; $R^2$ and $R^3$ each are independently hydrogen or (lower)alkyl, or, when $R^2$ is hydrogen, $R^3$ may be (lower)alkenyl, (lower)alkynyl, pyridylmethyl or



or a nontoxic pharmaceutically acceptable salt, hydrate or solvate thereof.

13. A composition of any one of Claims 1 - 12 wherein the dosage of pepstatin is from about 100 to about 175 mg and the dosage of the compound of Formula I is from about 2 to about 100 mg.

14. A composition of Claim 13 wherein the dosage of the compound of Formula I is from about 4 to about 50 mg.

15. A pharmaceutical composition of claim 13 which comprises from about 100 to 175 mg of pepstatin and from about 2 to about 15 mg of 3-amino-4-{2-[(5-dimethylaminomethyl-2-furyl)-methylthio]-ethylamino}-1,2,5-thiadiazole 1-oxid or a non-toxic pharmaceutically acceptable acid addition salt, hydrate or solvate thereof.

16. A pharmaceutical composition of claim 13 which comprises from about 100 to about 175 mg of pepstatin and from about 2 to about 15 mg of 3-amino-4-{2-[(2-guanidinothiazol-4-yl)methylthio]ethylamino}-1,2,5-thiadiazole 1-oxide or a nontoxic pharmaceutically acceptable acid addition salt, hydrate or solvate thereof.

17. A composition of Claims 13 to 16 wherein the pepstatin is in the form of pepstatin floating mini-capsules.

18. A composition of anyone of claims 1 - 17 in unit dosage form.

19. Use of at least one compound of the formula I of anyone of claims 1 - 11 in combination with pepstatin for the treatment of peptic ulcers.

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FIG. 1

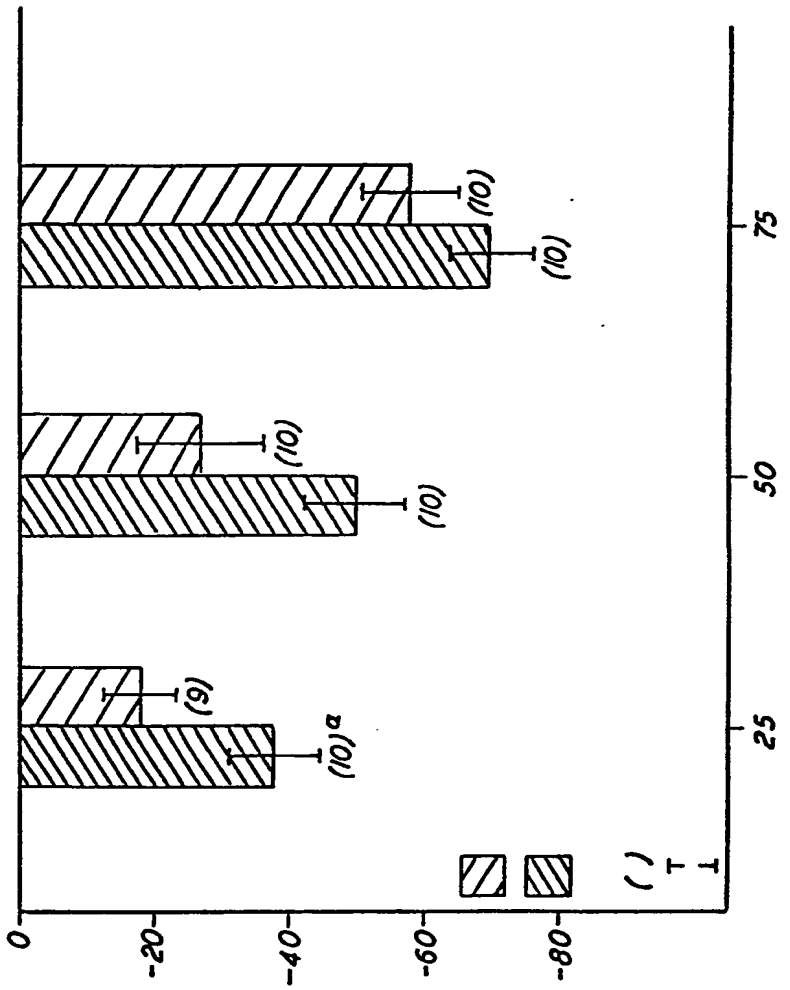

FIG. 2

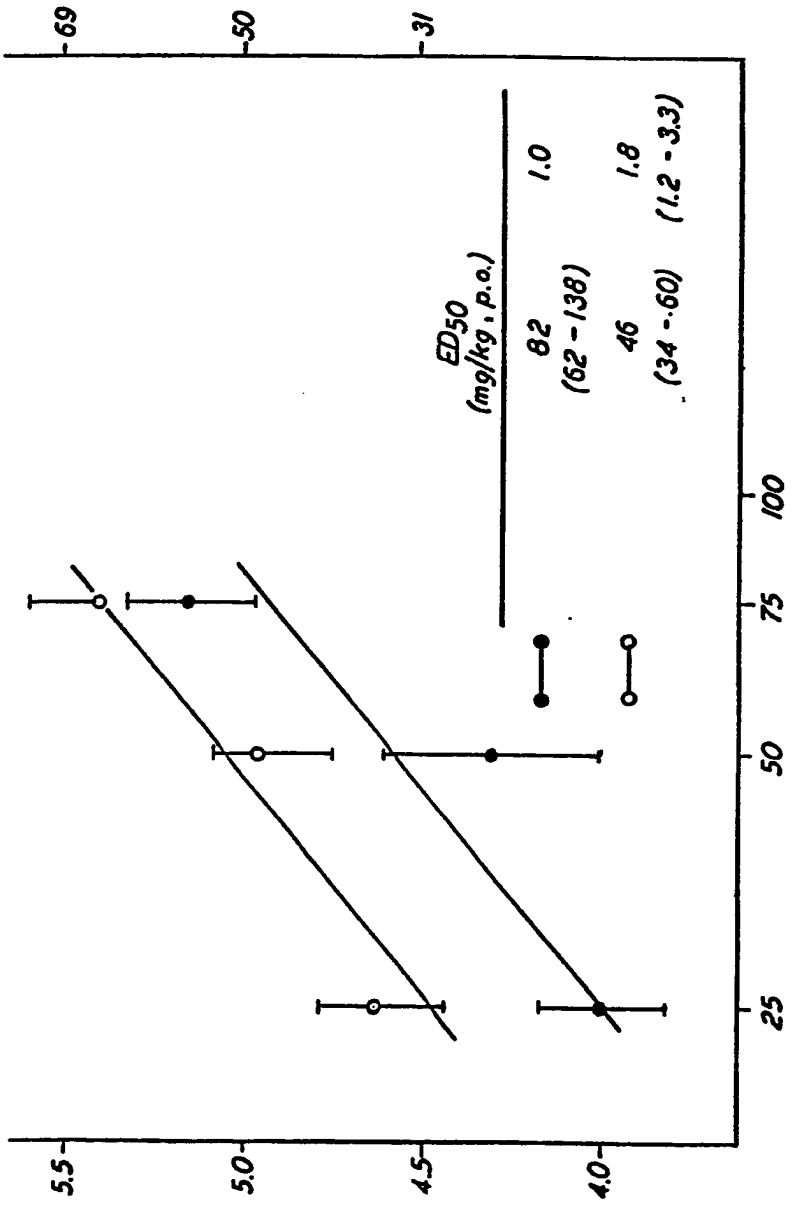
69
50
31
ED50 (mg/kg ; p.o.)
82 (62 - 138)
1.0
46 (34 - 60)
1.8 (1.2 - 3.3)
100
75
50
25
5.5
5.0
4.5
4.0

FIG. 3

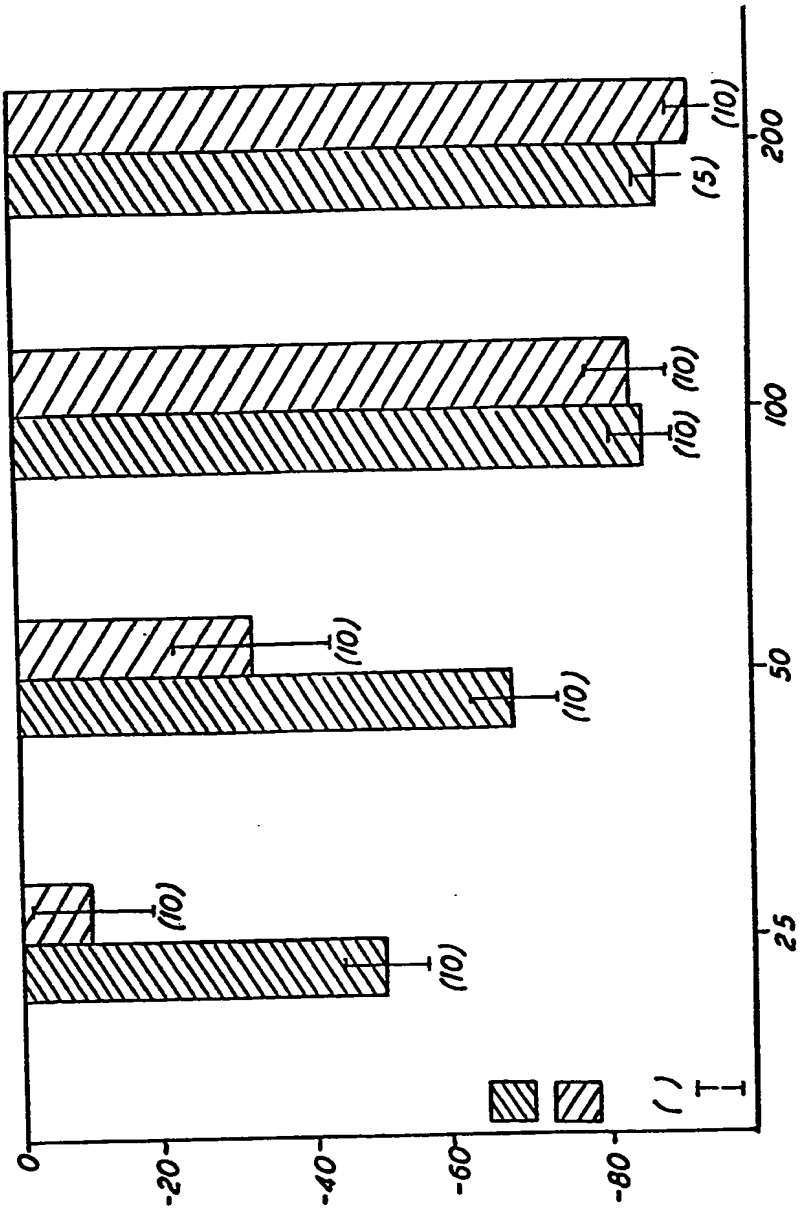

FIG.4

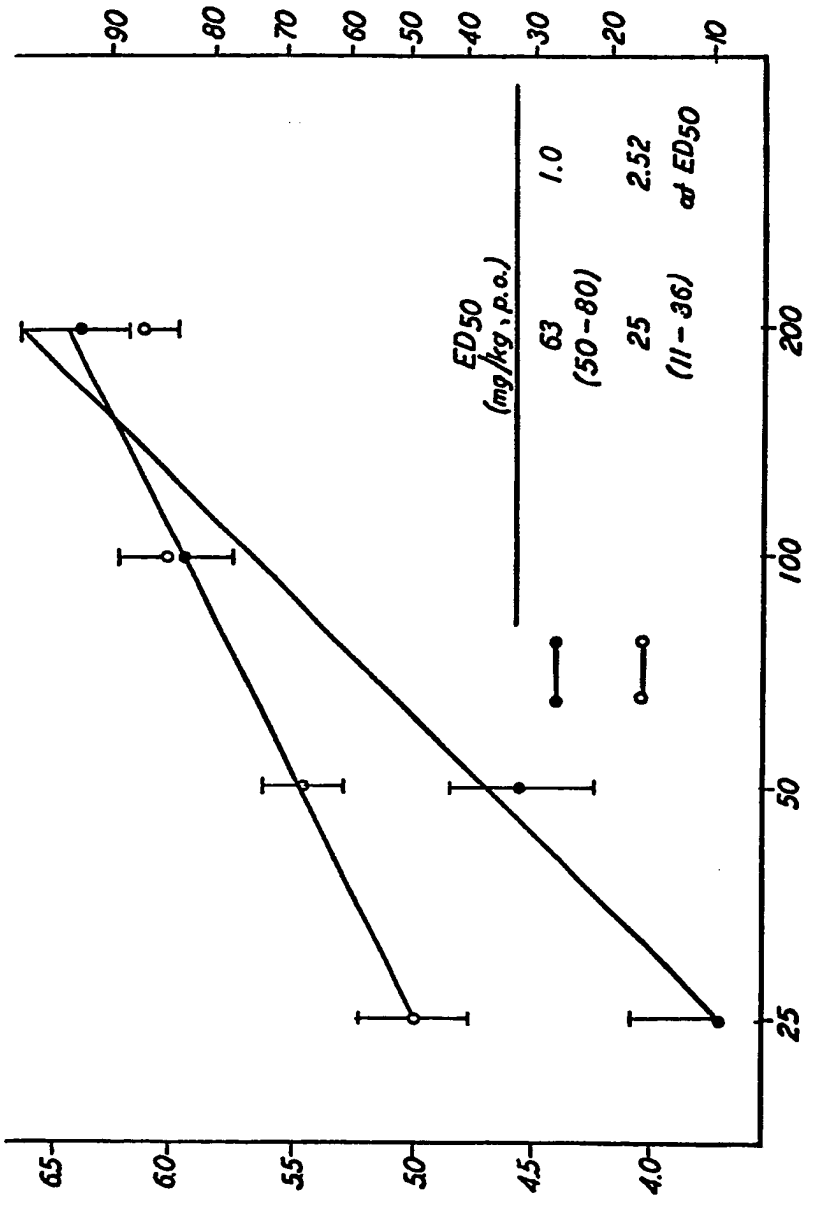
-90
-80
-70
-60
-50
-40
-30
-20
-10
65
60
55
50
45
40
25
50
100
200
ED50 (mg/kg, p.o.)
63 (50-80)
25 (11-36)
1.0
2.52
of ED50

FIG.5

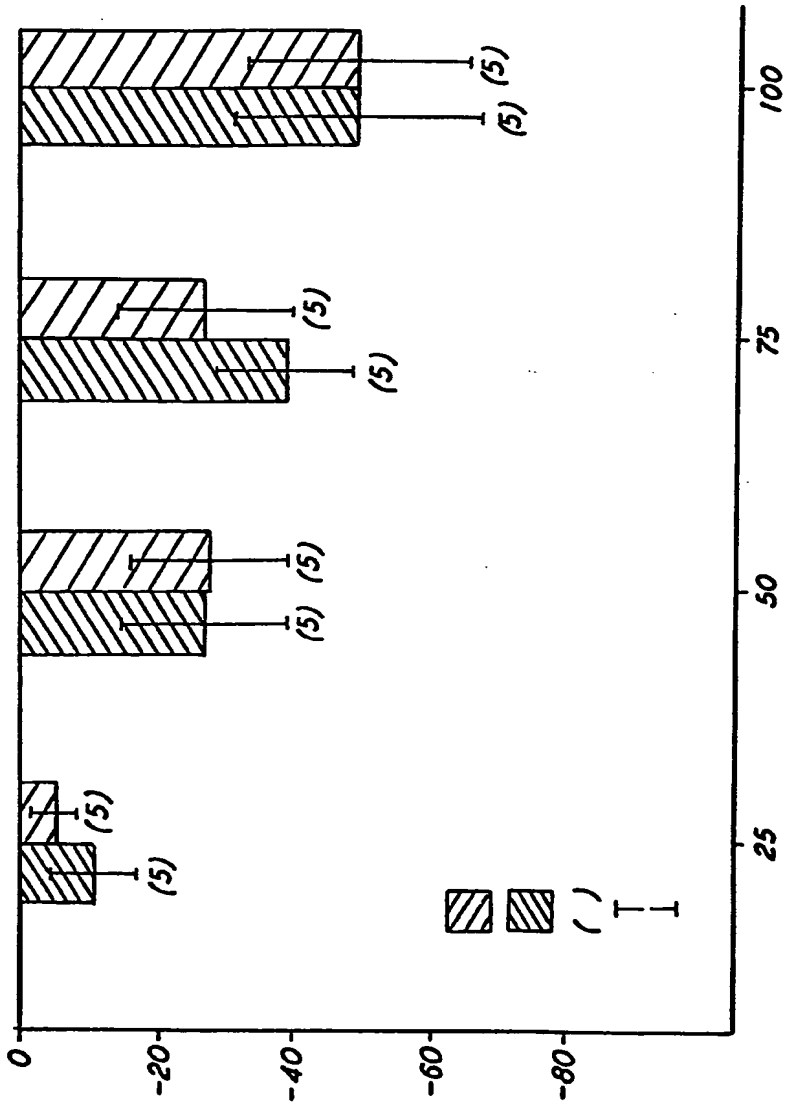

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FIG. 6